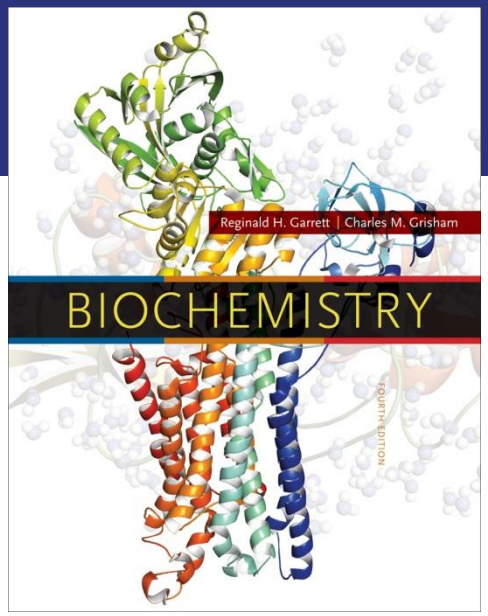
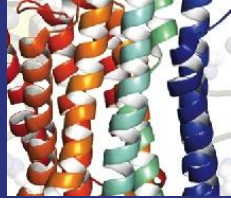


Reginald H. Garrett
Charles M. Grisham

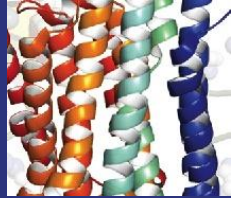
Chapter 24
Lipid Biosynthesis

Outline



- How are fatty acids synthesized?
- How are complex lipids synthesized?
- How are eicosanoids synthesized, and what are their functions?
- How is cholesterol synthesized?
- How are lipids transported throughout the body?
- How are bile acids biosynthesized?
- How are steroid hormones synthesized and utilized?

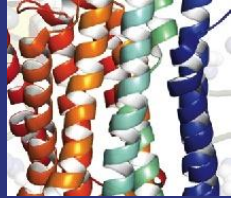
24.1 – How Are Fatty Acids Synthesized?



The Biosynthesis and Degradation Pathways are Different

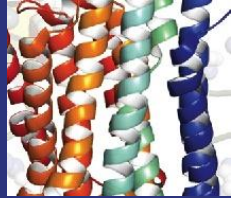
- As in cases of glycolysis/gluconeogenesis and glycogen synthesis/breakdown, fatty acid synthesis and degradation go by different routes
- There are four major differences between fatty acid breakdown and biosynthesis

The Differences Between Fatty Acid Biosynthesis and Fatty Acid Breakdown



1. Intermediates in synthesis are linked to -SH groups of **acyl carrier proteins** (as compared to -SH groups of CoA)
2. Synthesis in **cytosol**; breakdown in mitochondria
3. Enzymes of synthesis are one polypeptide, the **fatty acid synthase**
4. Biosynthesis uses **$NADPH/NADP^+$**; breakdown uses $NADH/NAD^+$

Formation of Malonyl-CoA Activates Acetate Units for Fatty Acid Synthesis



- The design strategy for fatty acid synthesis:

1) Fatty acid chains are constructed by the addition of two-carbon units derived from acetyl-CoA

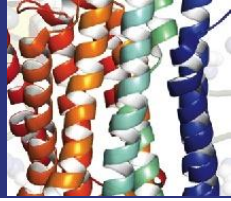
2) The acetate units are activated by formation of **malonyl-CoA** (at the expense of ATP)

3) The addition of two-carbon units to the growing chain is driven by decarboxylation of malonyl-CoA

4) The elongation reactions are repeated until the growing chain reaches 16 carbons in length (palmitic acid)

5) Other enzymes then add double bonds and additional carbon units to the chain

Cells Provide Cytosolic Acetyl-CoA and NADPH for Fatty Acid Synthesis



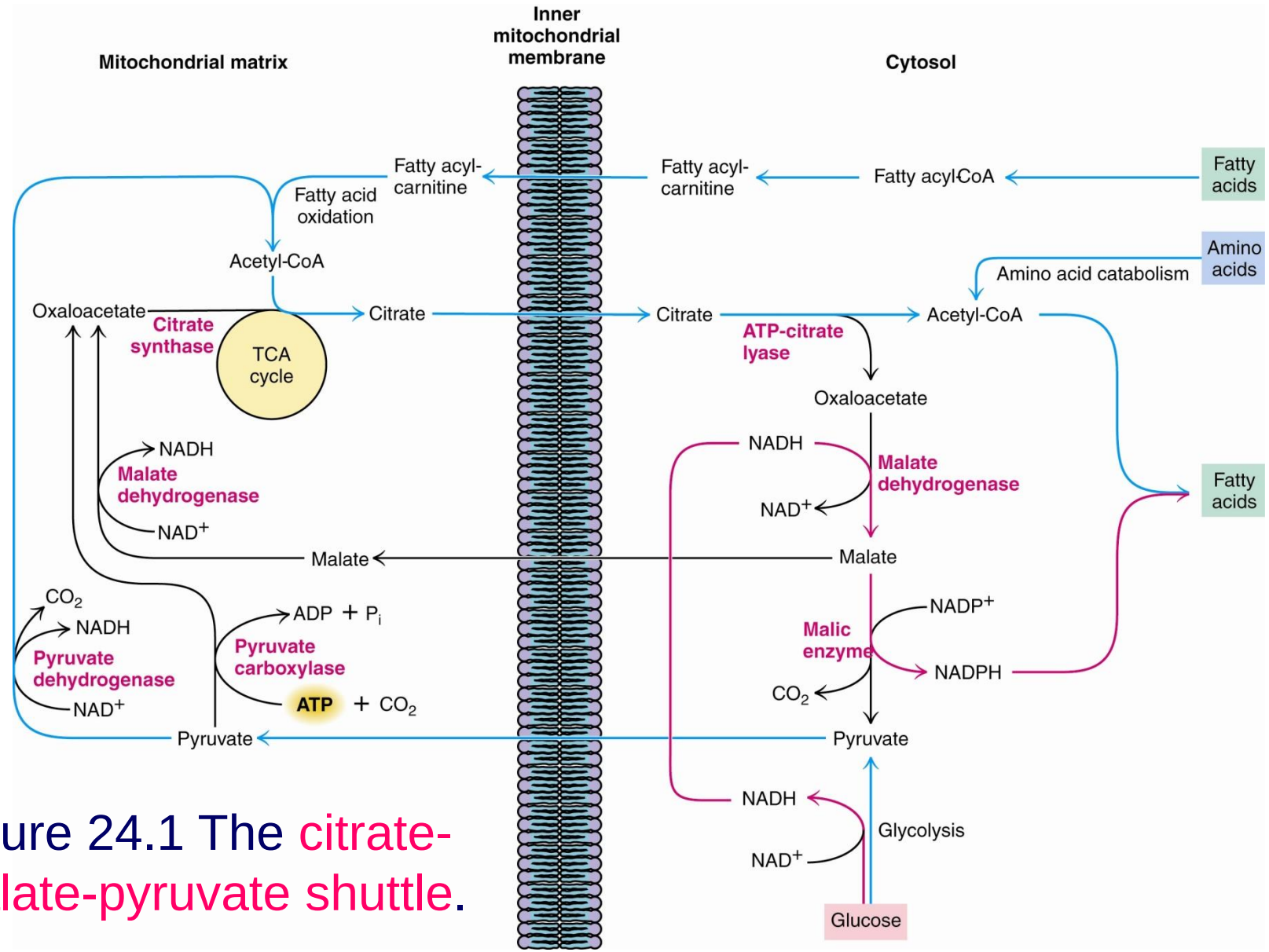
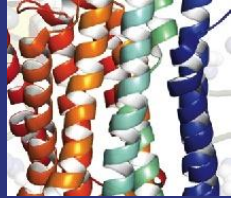


Figure 24.1 The citrate-malate-pyruvate shuttle.

Carboxylation of Acetyl-CoA to Form Malonyl-CoA is Catalyzed by Acetyl-CoA Carboxylase



The "ACC enzyme" commits acetate to fatty acid synthesis

- Carboxylation of acetyl-CoA to form malonyl-CoA is the *irreversible*, **committed step** in fatty acid biosynthesis
- ACC uses **bicarbonate** and **ATP** (AND **biotin**)
- *E.coli* enzyme has three subunits
- Animal enzyme is one polypeptide with all three functions:
  - **biotin carboxyl carrier protein**
  - **biotin carboxylase**
  - **carboxyltransferase**

Acetate Units Are Committed to Fatty Acid Synthesis by Formation of Malonyl-CoA

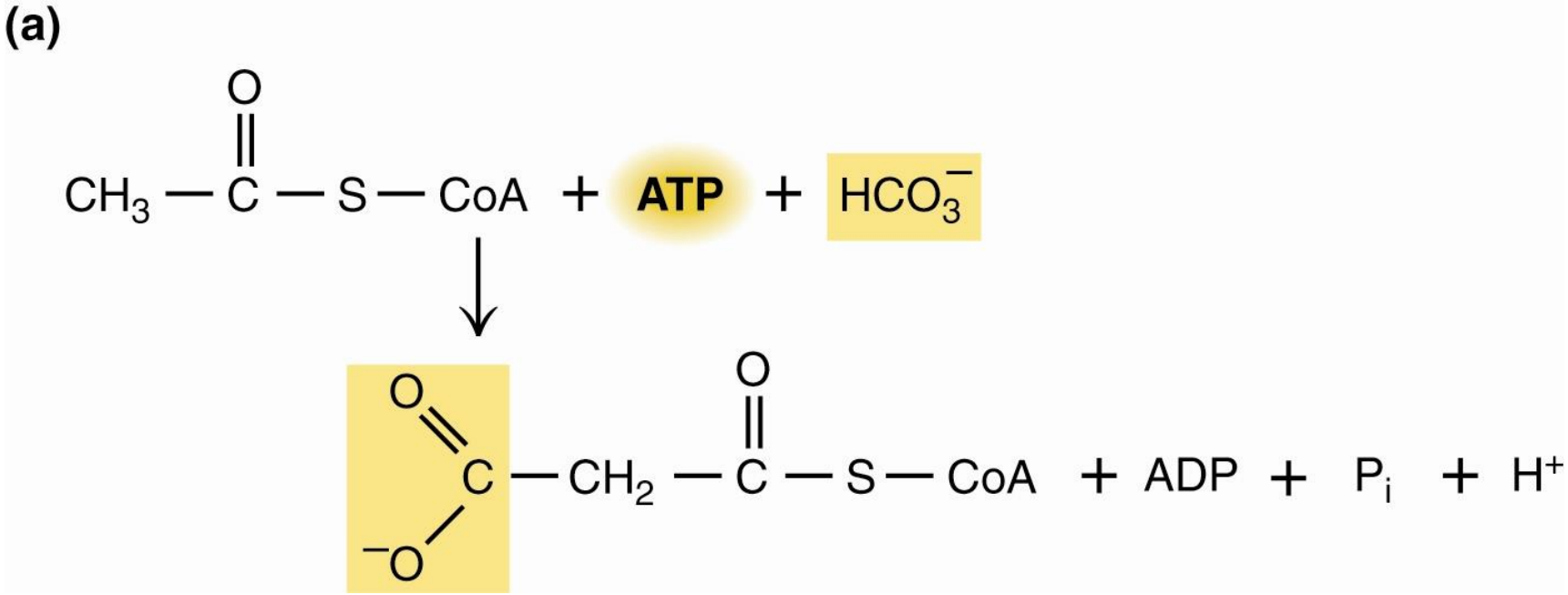
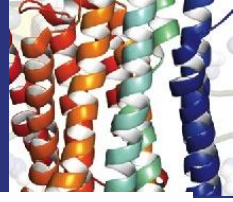


Figure 24.2a The acetyl-CoA carboxylase reaction produces malonyl-CoA for fatty acid synthesis.

Acetate Units Are Committed to Fatty Acid Synthesis by Formation of Malonyl-CoA



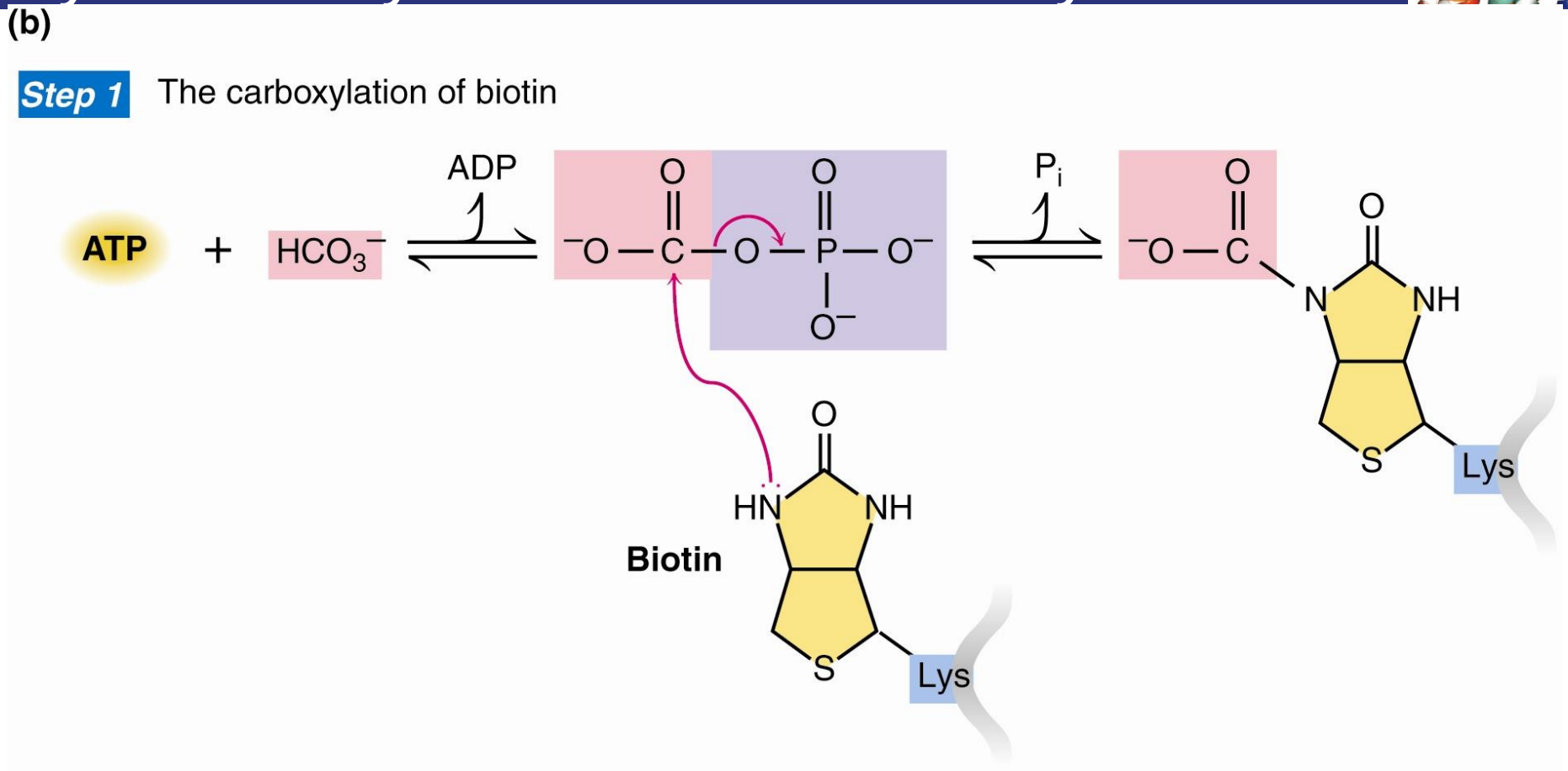
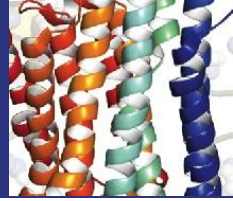


Figure 24.2b A mechanism for the acetyl-CoA carboxylase reaction. Bicarbonate is activated for carboxylation reactions by formation of N-carboxybiotin. ATP drives the reaction forward, with transient formation of a carbonylphosphate intermediate.

Acetate Units Are Committed to Fatty Acid Synthesis by Formation of Malonyl-CoA



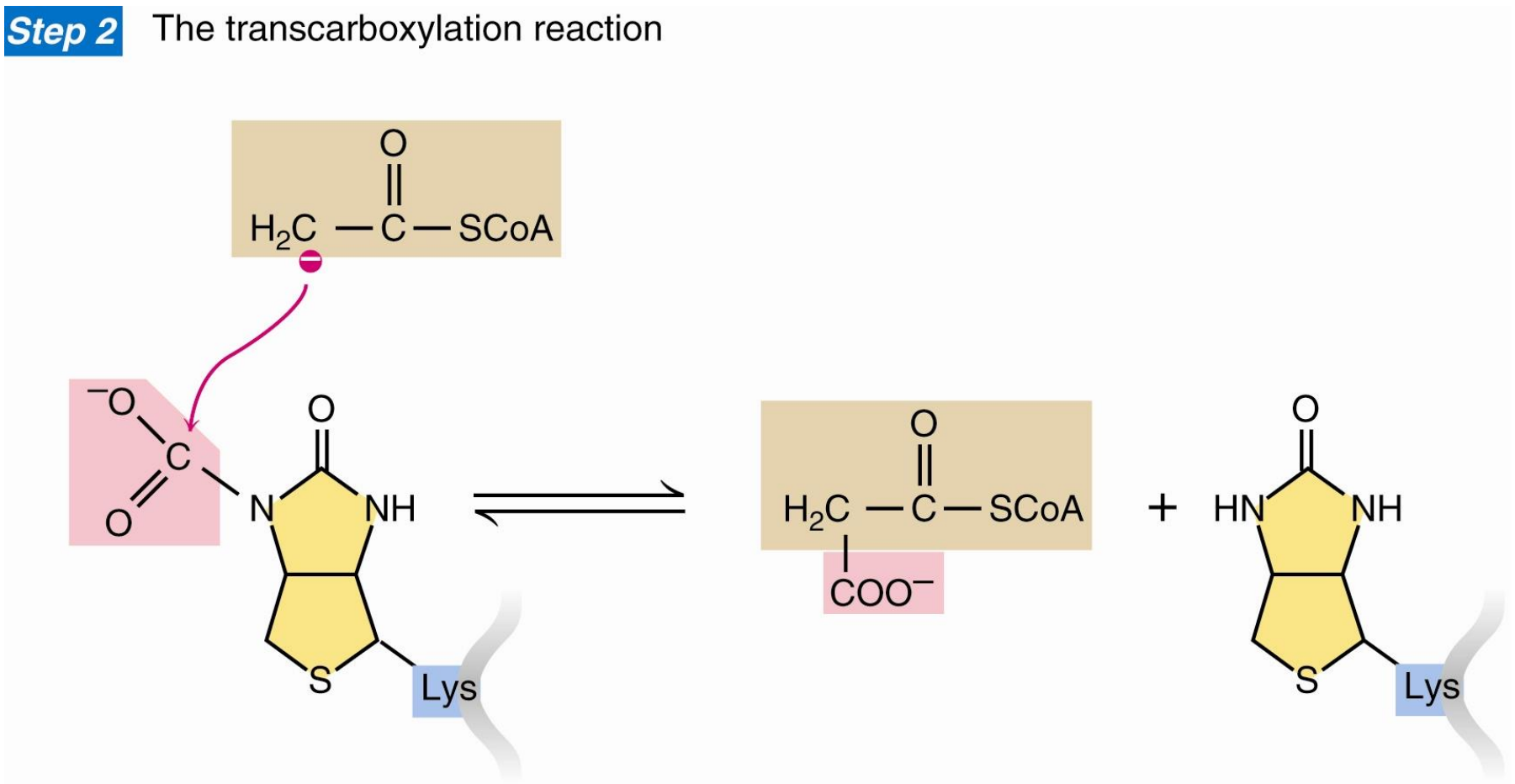
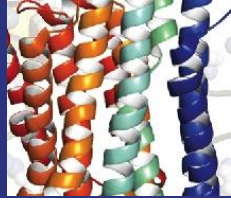


Figure 24.2 In a typical biotin-dependent reaction, nucleophilic attack by the acetyl-CoA carbanion on the carboxyl carbon of N-carboxybiotin – a transcarboxylation – yields the carboxylated product.

Acetyl-CoA Carboxylase in *E. coli* Consists of Three Subunits



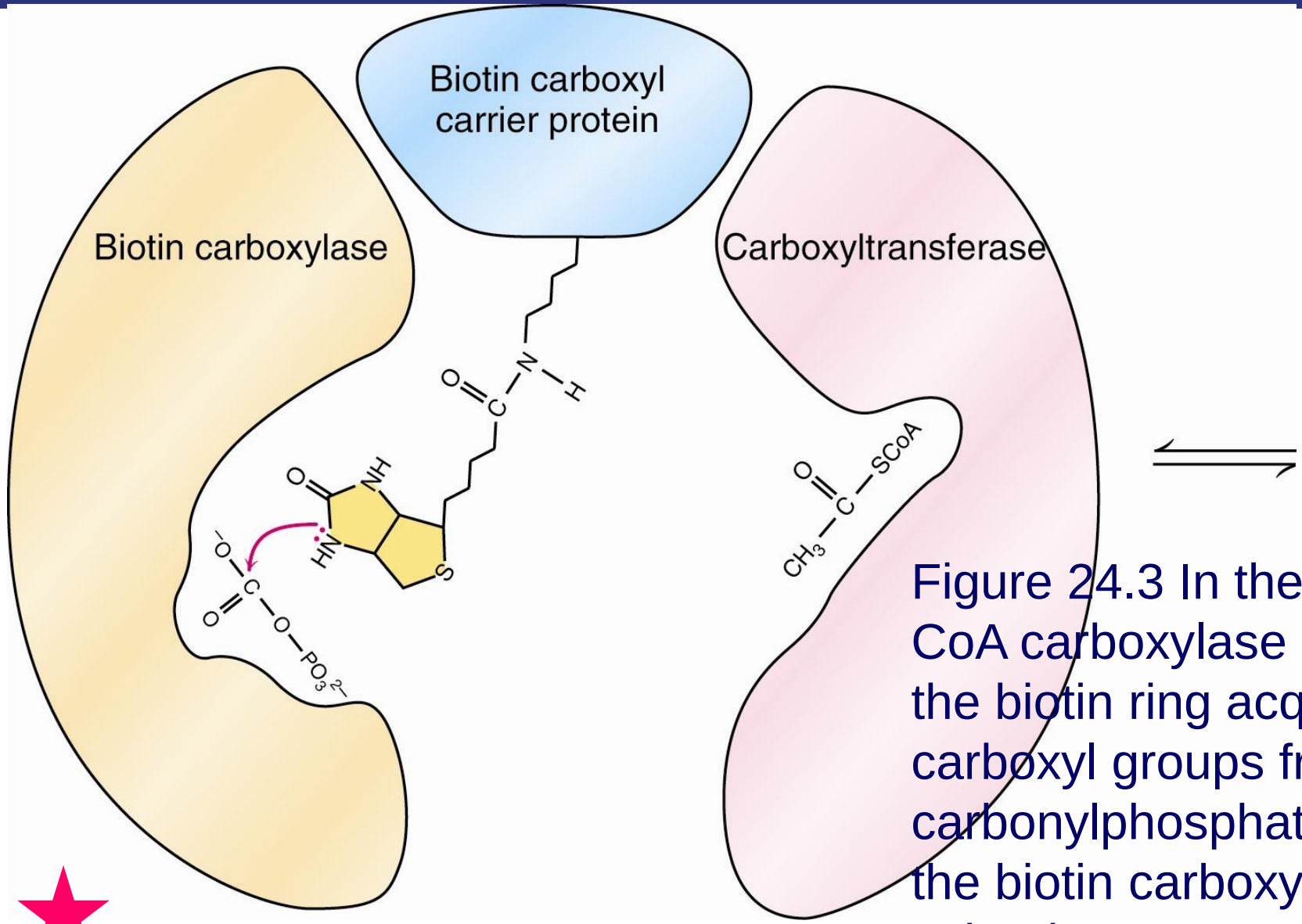
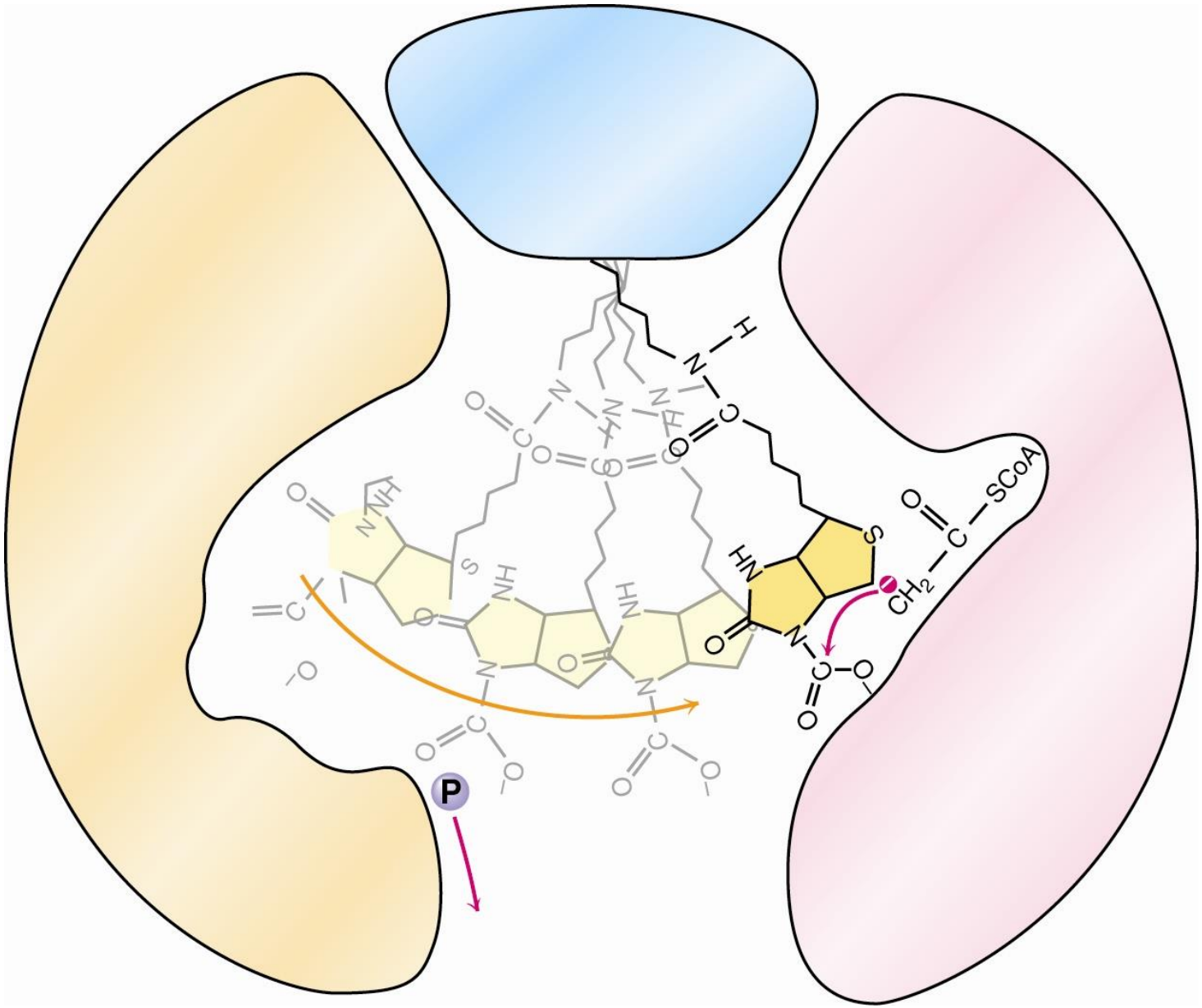
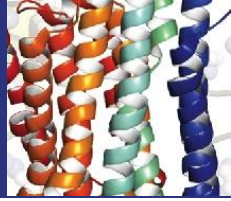


Figure 24.3 In the acetyl-CoA carboxylase reaction, the biotin ring acquires carboxyl groups from carbonylphosphate on the biotin carboxylase subunit.

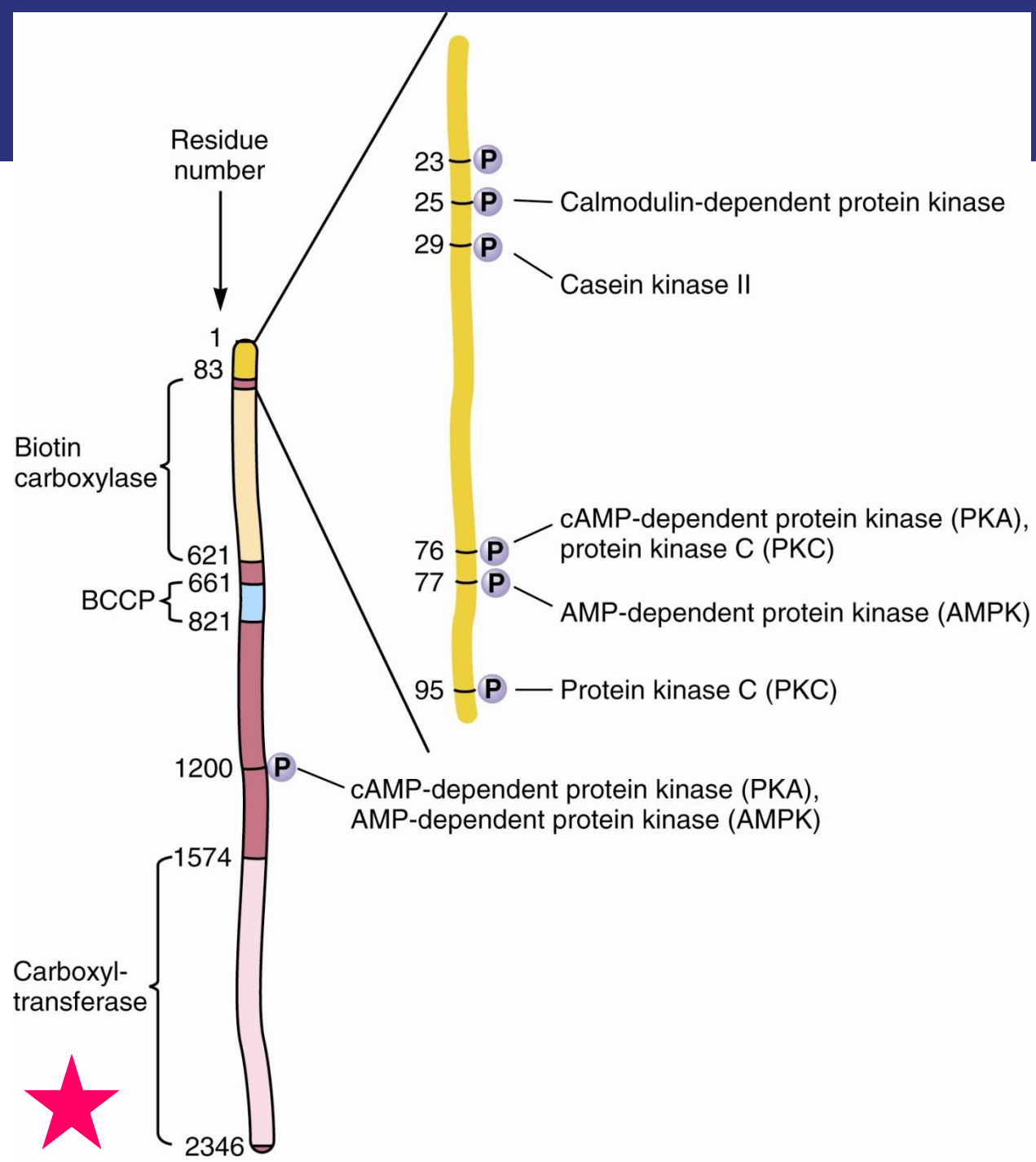
Figure 24.3 Biotin on a flexible tether delivers carboxyl groups from the carboxylase to the carboxyltransferase.



Acetyl-CoA Carboxylase in Animals is a Multifunctional Protein



- In animals, acetyl-CoA carboxylase (ACC) is a long, active filamentous polymer formed from inactive protomers
- Each of these protomers contains the biotin carboxyl carrier moiety, biotin carboxylase, and carboxyl transferase
- As a committed step, ACC is carefully regulated
- Palmitoyl-CoA (product) favors monomers
- Citrate favors the active polymeric form
- Phosphorylation modulates/ citrate activation and palmitoyl-CoA inhibition



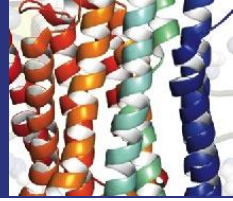


Figure 24.4 Schematic of the acetyl-CoA carboxylase, with domains and phosphorylation sites indicated, along with the protein kinases responsible.

ACC Phosphorylation Modulates Activation by Citrate and Inhibition by Palmitoyl-CoA

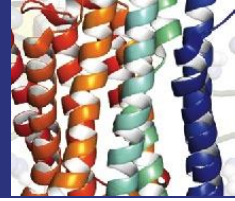
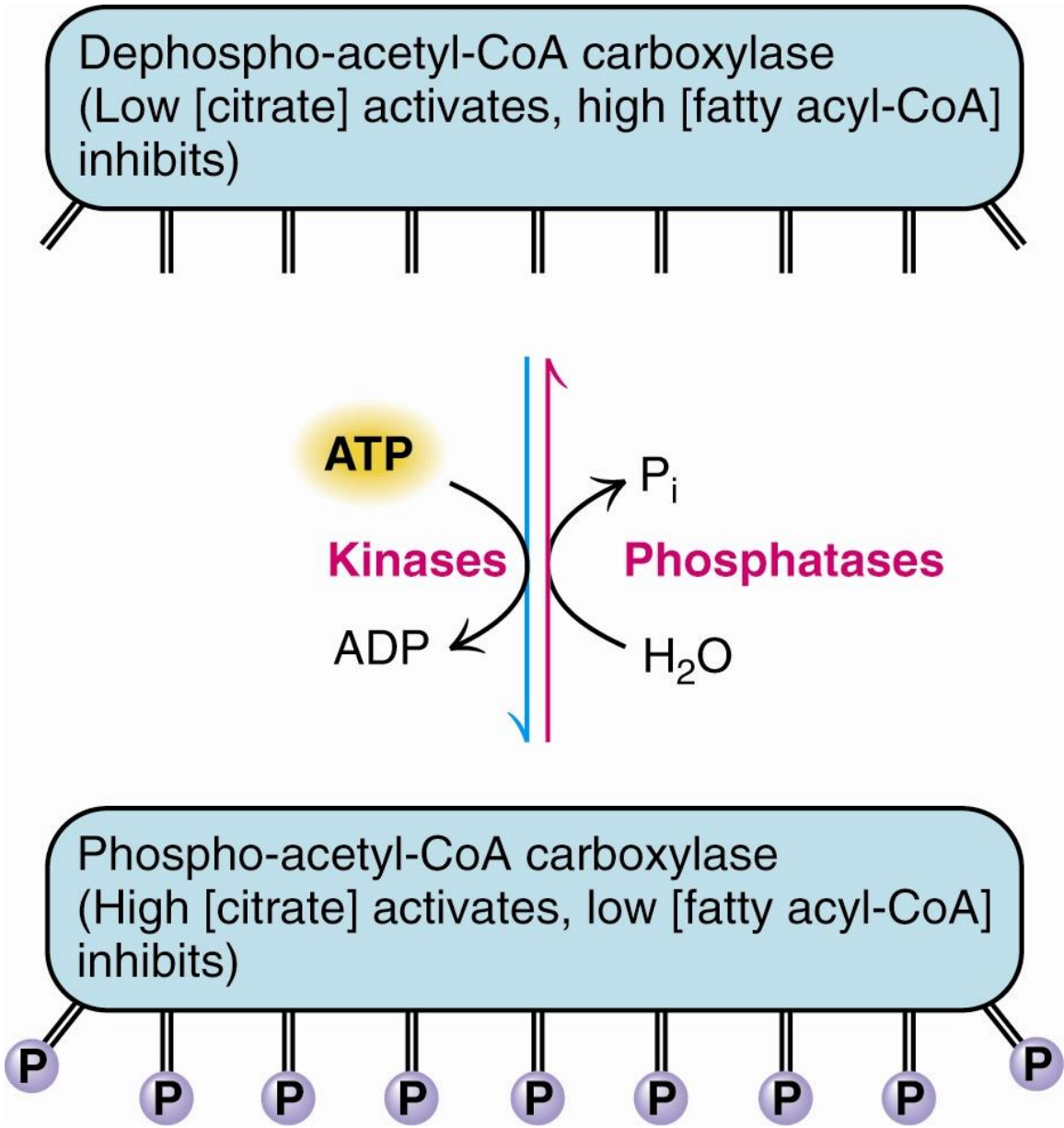
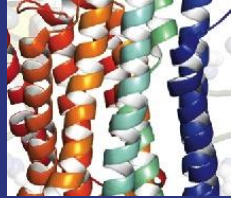


Figure 24.5 The activity of acetyl-CoA carboxylase is modulated by phosphorylation. The dephospho form of the enzyme is activated by low [citrate] and inhibited only by high levels of fatty acyl-CoA. In contrast, the phosphorylated enzyme is activated by high levels of citrate.

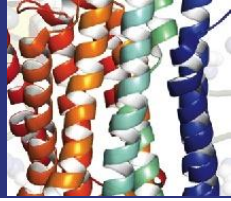


In Animals, Fatty Acid Synthesis Takes Place in Multienzyme Complexes



- Fatty acid synthesis in mammals occurs on homodimeric **fatty acyl synthase I (FAS I)**
- Which consists of 270 kD polypeptides which contain all reaction centers required to produce a fatty acid
- In yeast and fungi (lower eukaryotes), the activities of FAS are distributed on two multifunctional peptide chains
- In plants and bacteria, the enzymes of FAS are separated and independent, and this collection of enzymes is referred to as **fatty acid synthase II** (**FAS II)**

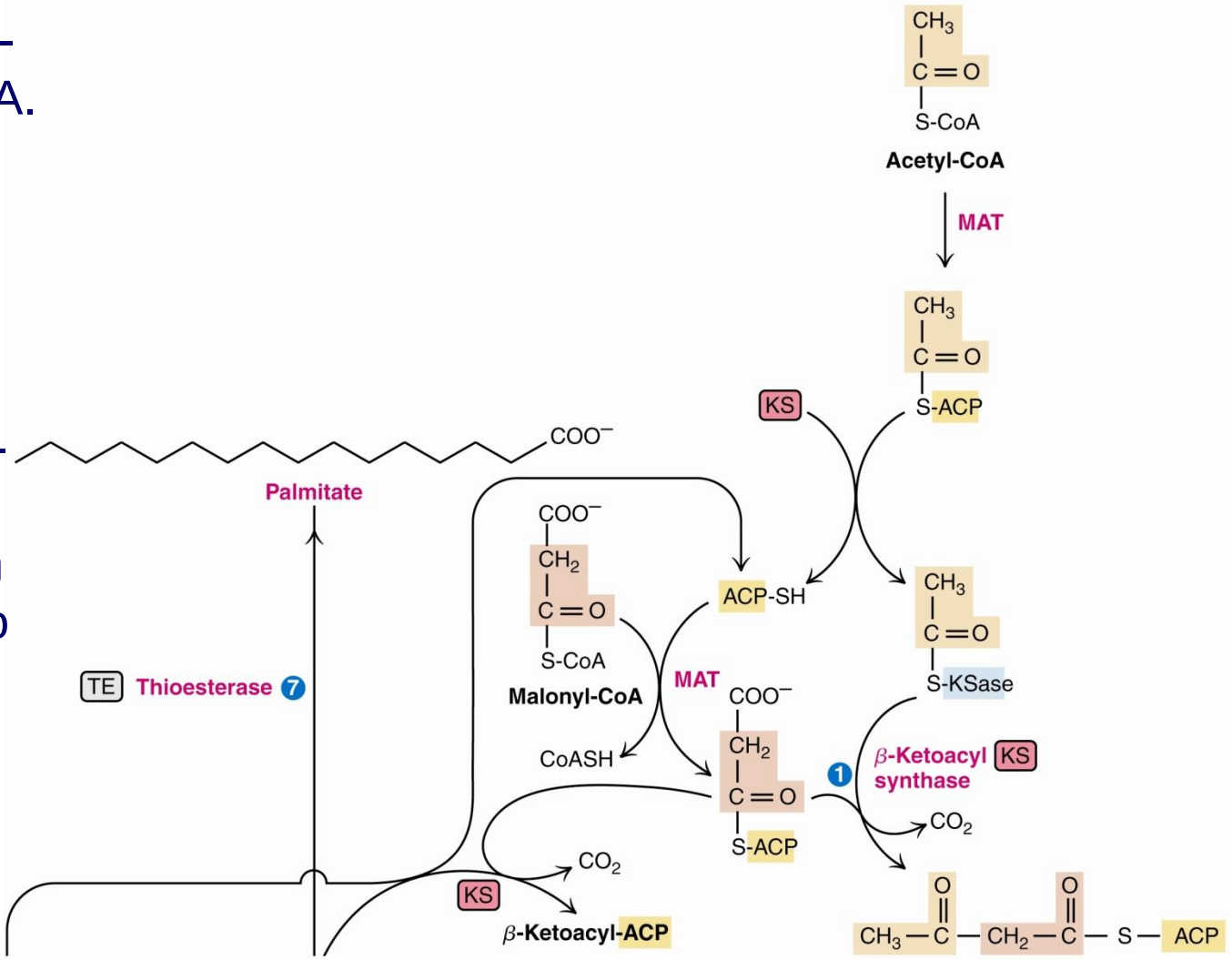
Acyl Carrier Proteins Carry the Intermediates in Fatty Acid Synthesis



- The individual steps of fatty acid synthesis are similar across all organisms
- The mammalian pathway (Figure 24.7) is a cycle of elongation that involves six enzyme activities
- Elongation is initiated by transfer of the acyl moiety of acetyl-CoA to the acyl carrier protein by the **malonyl-CoA-acetyl-CoA-ACP transacylase (MAT)**
- This enzyme also transfers the malonyl group of malonyl-CoA to ACP (Figure 24.7)

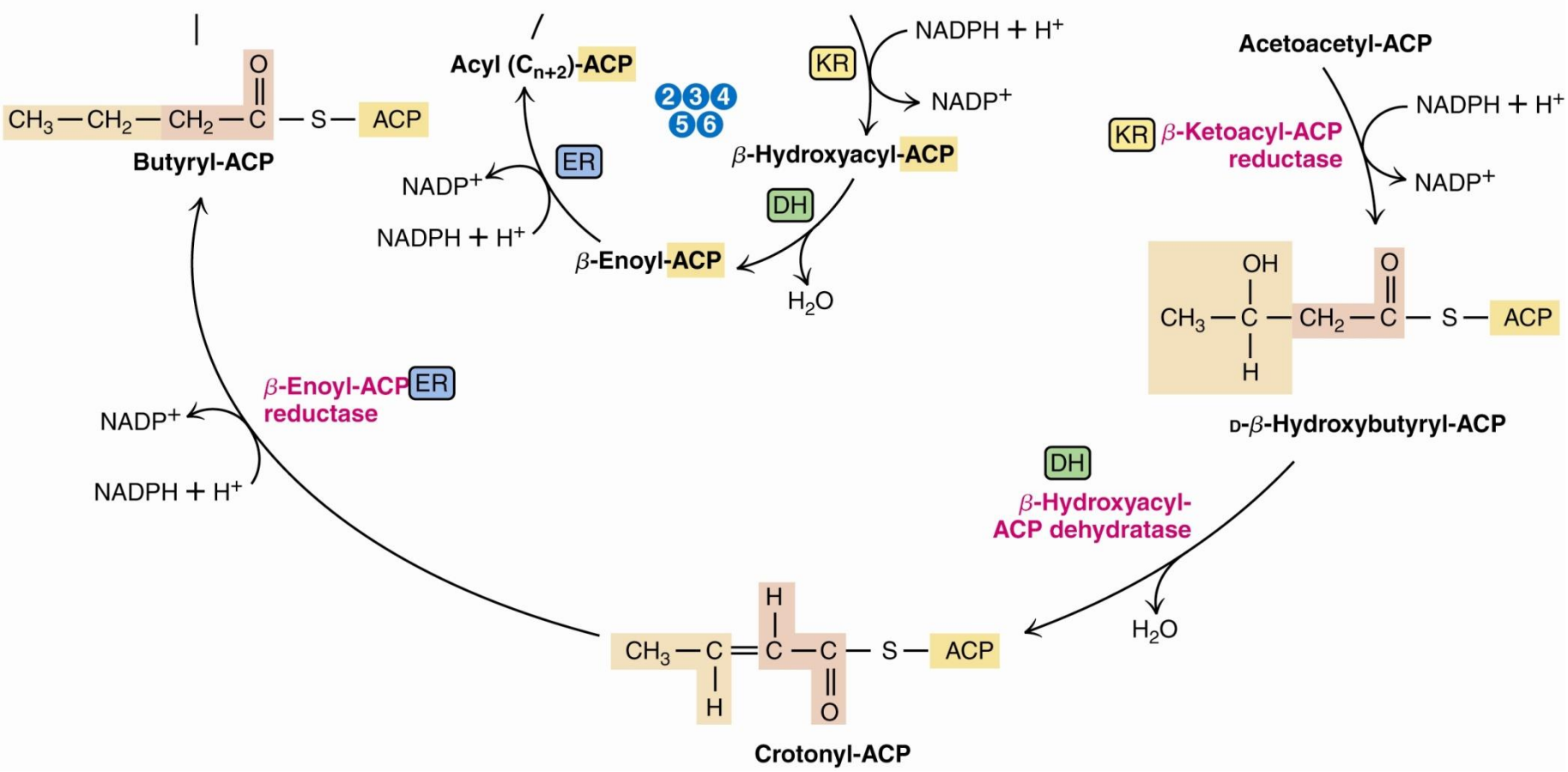
Decarboxylation Drives the Condensation of Acetyl-CoA and Malonyl-CoA

Figure 24.7 The pathway of palmitate synthesis from acetyl-CoA and malonyl-CoA. Acetyl and malonyl building blocks are introduced as ACP conjugates. Decarboxylation drives the β-ketoacyl-ACP-synthase and results in the addition of two-carbon units to the growing chain.



The Pathway of Palmitate Synthesis From Acetyl-CoA and Malonyl-CoA

Figure 24.7 The first turn of the cycle begins at “1” and goes to butyryl-ACP; subsequent turns of the cycle are indicated as “2” through “6”.



Structure of the Fungal Fatty Acid Synthase

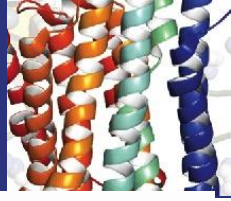
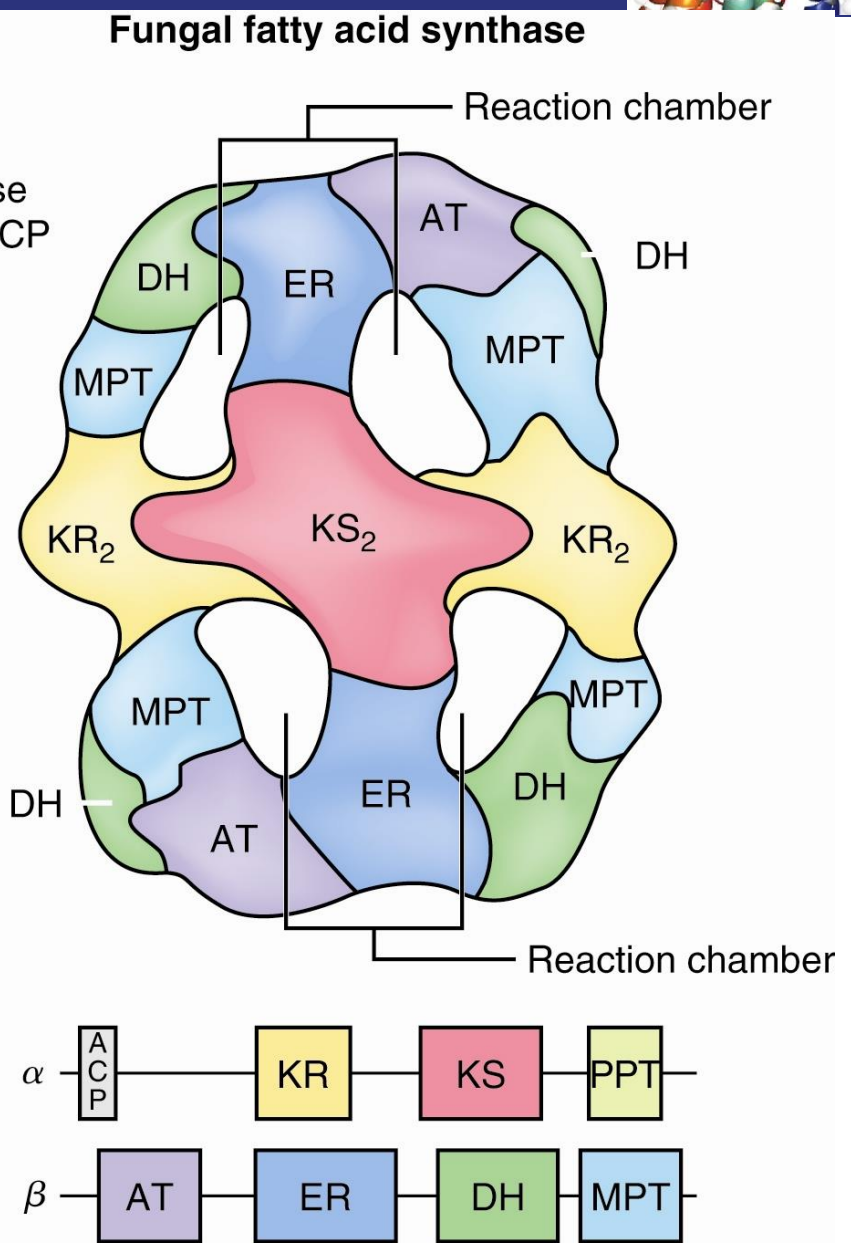


Figure 24.9 Fungal FAS is a closed barrel. The arrangement of the functional domains along the FAS α and β polypeptides is shown at the bottom.

AT: Acetyl transferase
MPT: Malonyl/palmitoyl transferase
MAT: Malonyl-CoA–acetyl-CoA-ACP transacylase
TE: Thioesterase
ACP: Acyl carrier protein
PPT: Phosphopantetheinyl transferase
KR: β-Ketoacyl reductase
KS: β-Ketoacyl synthase
ER: β-Enoyl reductase
DH: Dehydratase



Structure of Mammalian Fatty Acid Synthase

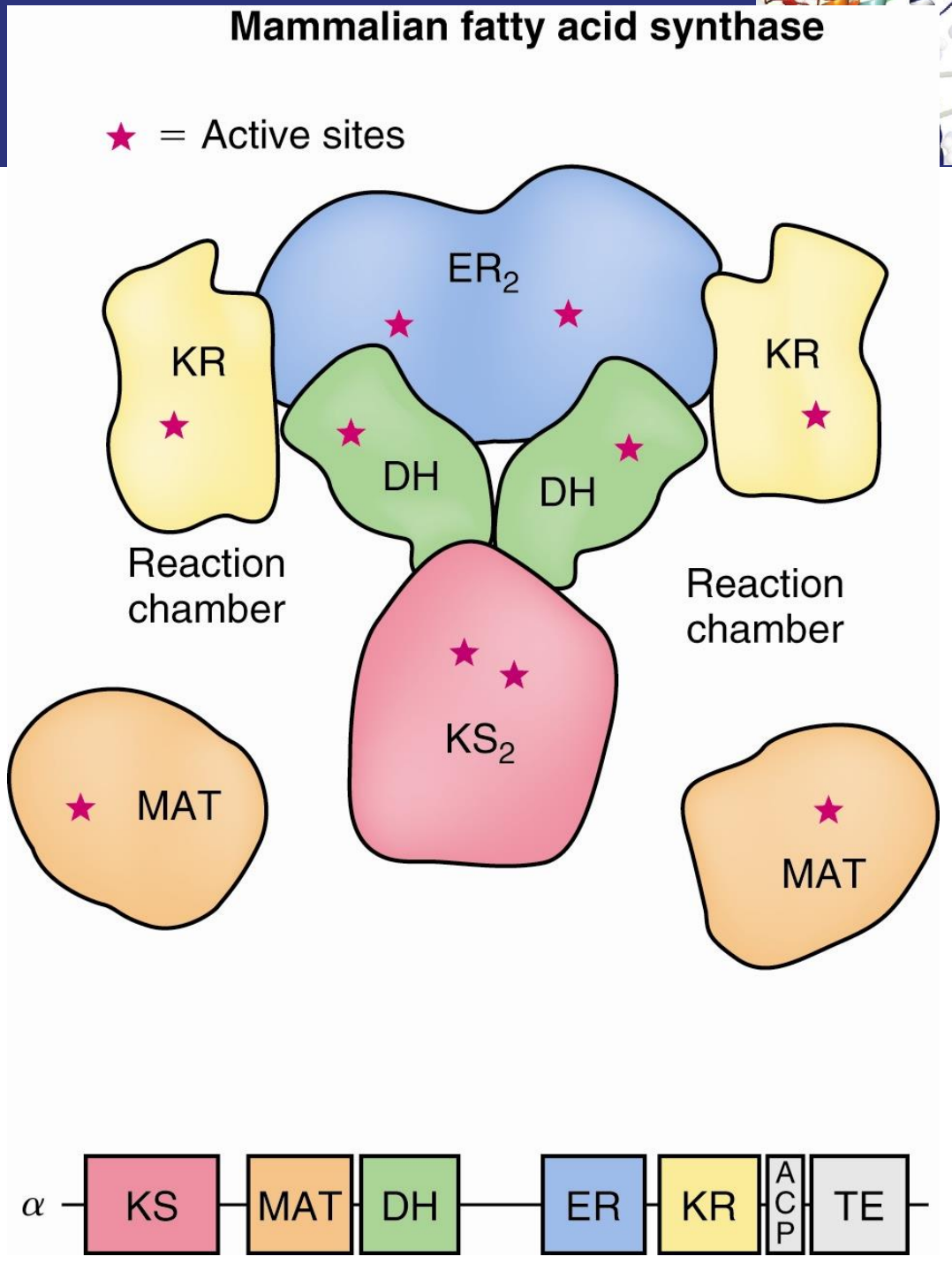
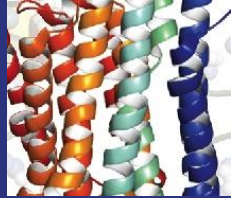


Figure 24.9 Mammalian FAS is an asymmetric X-shape. The arrangement of the functional domains along the FAS polypeptide is shown at the bottom.

C_{16} Fatty Acids May Undergo Elongation and Unsaturation



- Additional elongation - in mitochondria and ER
- Introduction of cis double bonds:
  - Prokaryotes use an O_2-independent process
  - Eukaryotes use an O_2-dependent process
- *E.coli* add double bonds while the site of attack is still near something functional (the thioester)
- Eukaryotes add double bond to middle of the chain - and need power of O_2 to do it

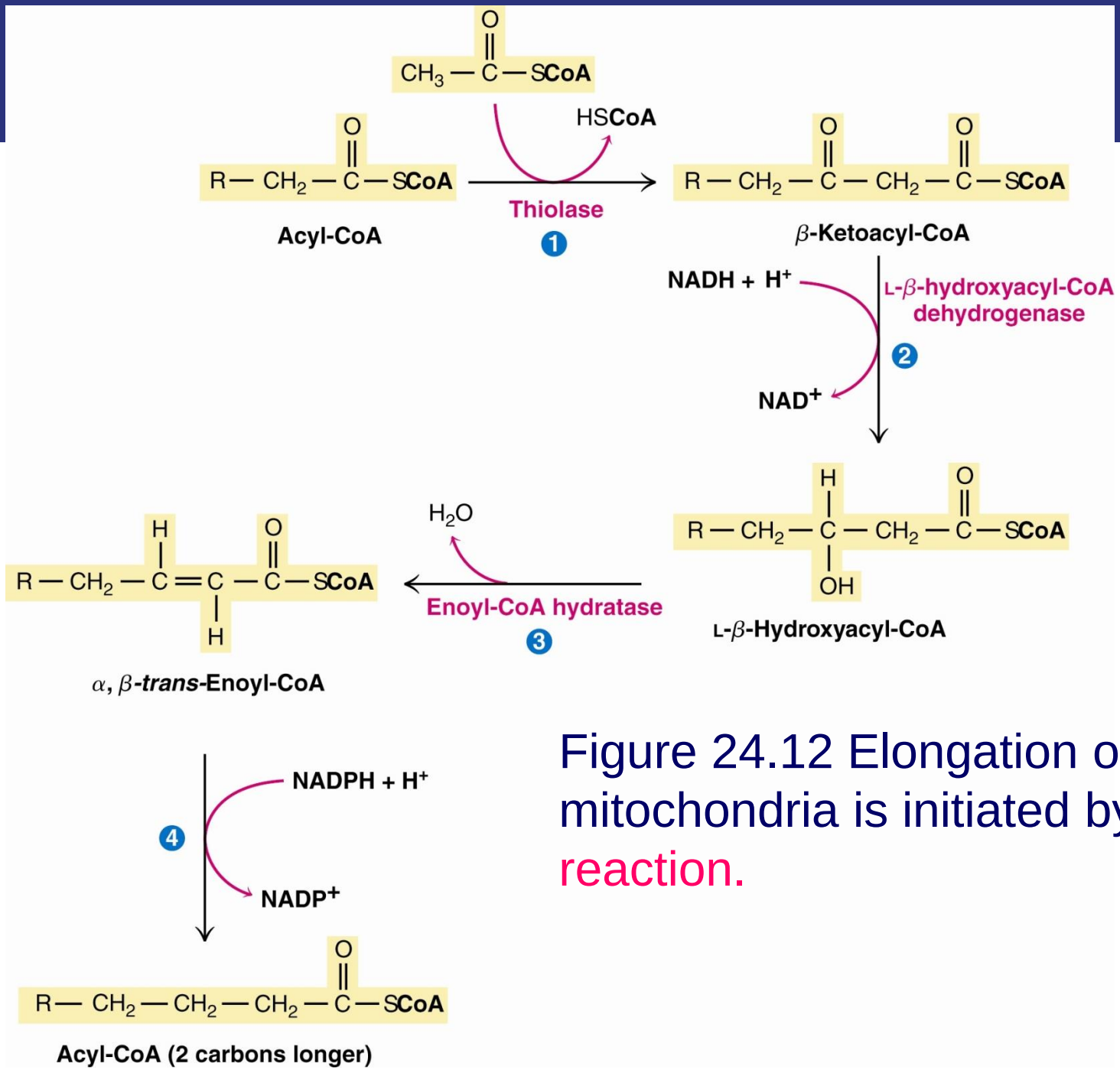
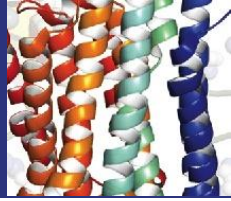


Figure 24.12 Elongation of fatty acids in mitochondria is initiated by the thiolase reaction.

Double Bond Formation in Prokaryotes



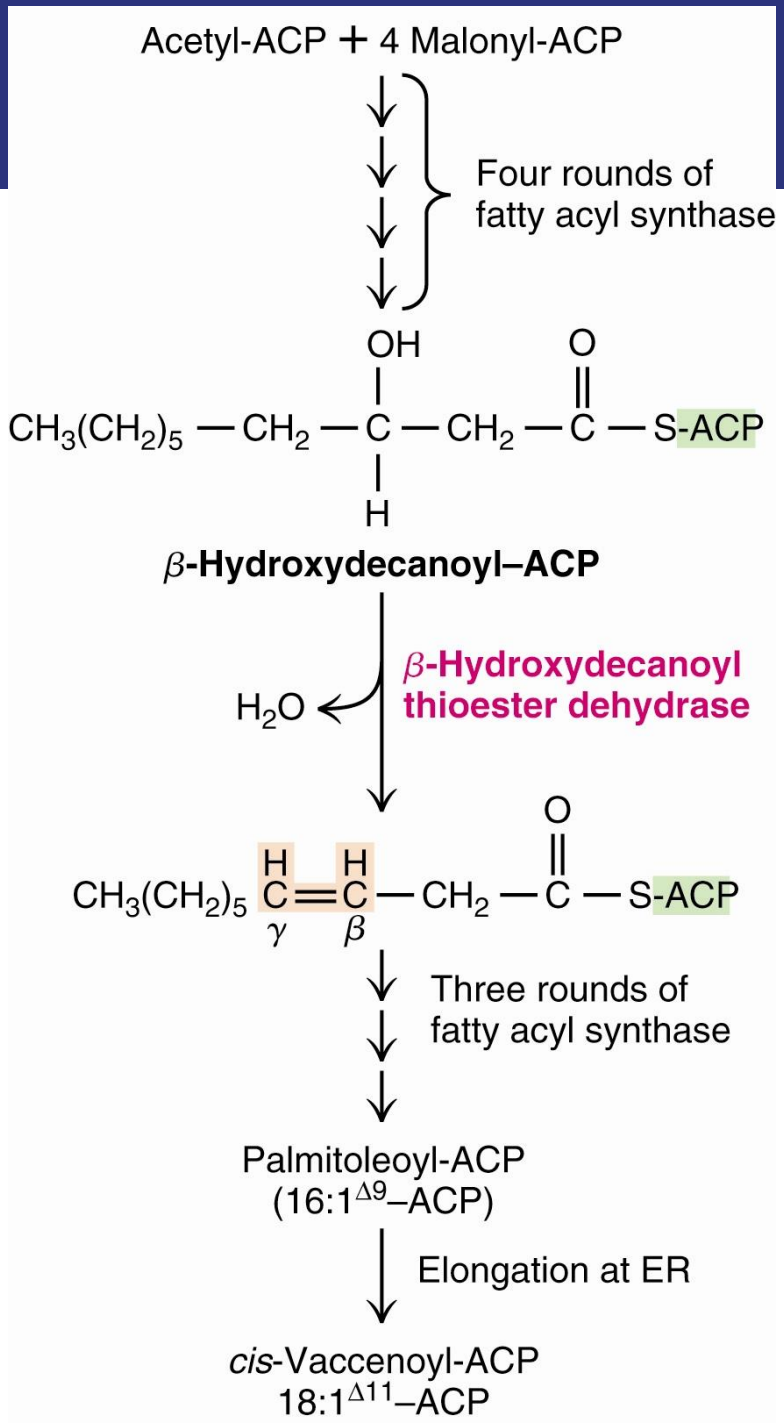
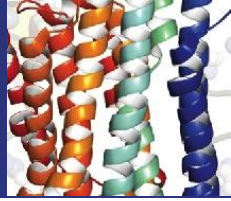


Figure 24.13 Double bonds are introduced into the growing fatty acid chain in *E. coli* by specific dehydrases. Palmitoleoyl-ACP is synthesized by a sequence of reactions involving four rounds of chain elongation, followed by double bound insertion by β-hydroxydecanoyl thioester dehydrase and three additional elongation steps. Another elongation cycle produces *cis*-vaccenic acid.

Unsaturation Reactions Occur in Eukaryotes in the Middle of an Aliphatic Chain



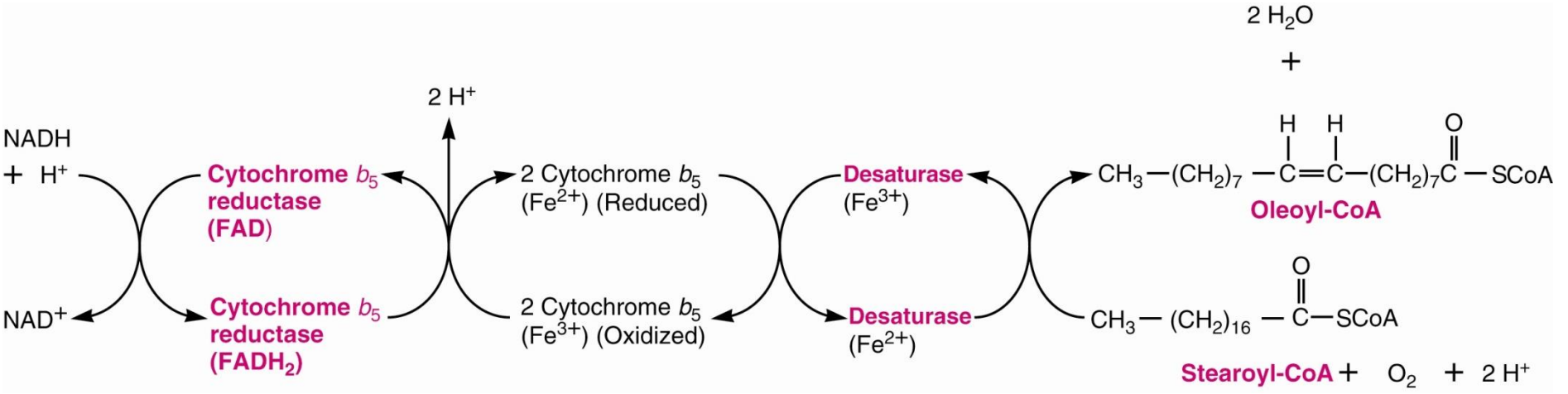
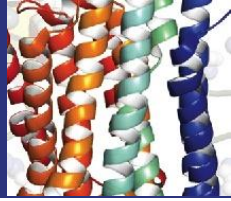
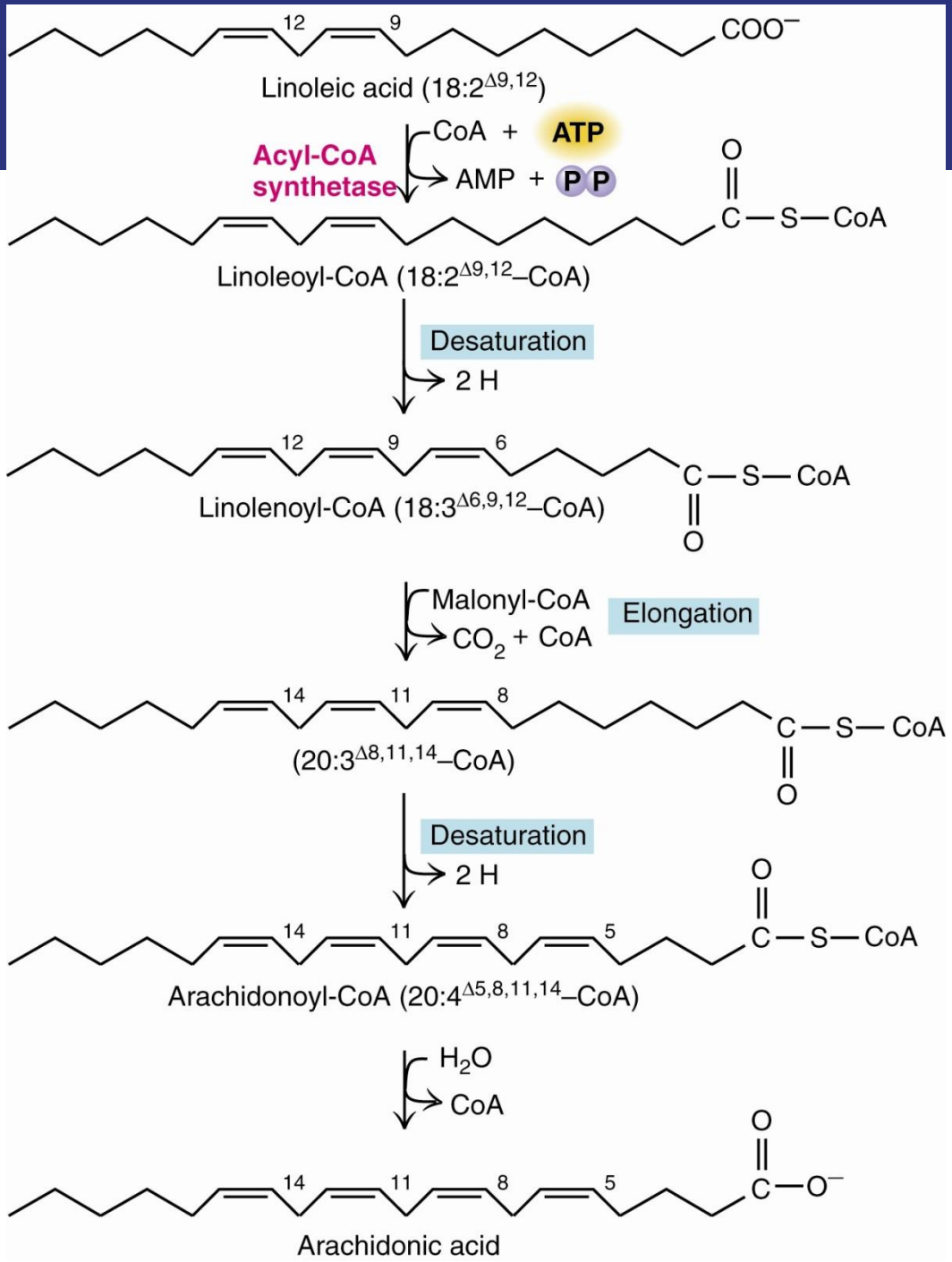


Figure 24.14 The conversion of stearoyl-CoA to oleoyl-CoA in eukaryotes is catalyzed by stearoyl-CoA desaturase in a reaction sequence that also involves cytochrome b_5 and cytochrome b_5 reductase. Two electrons are passed from NADH through the chain of reactions as shown, and two electrons are derived from the fatty acyl substrate.

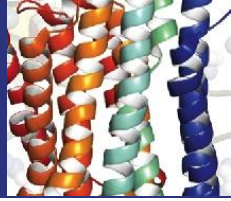




Arachidonic Acid Synthesis in Eukaryotes.

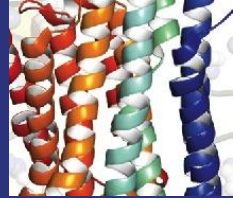
Arachidonic acid is synthesized from linoleic acid in eukaryotes. This is the means by which animals synthesize fatty acids with double bonds at positions other than C-9.

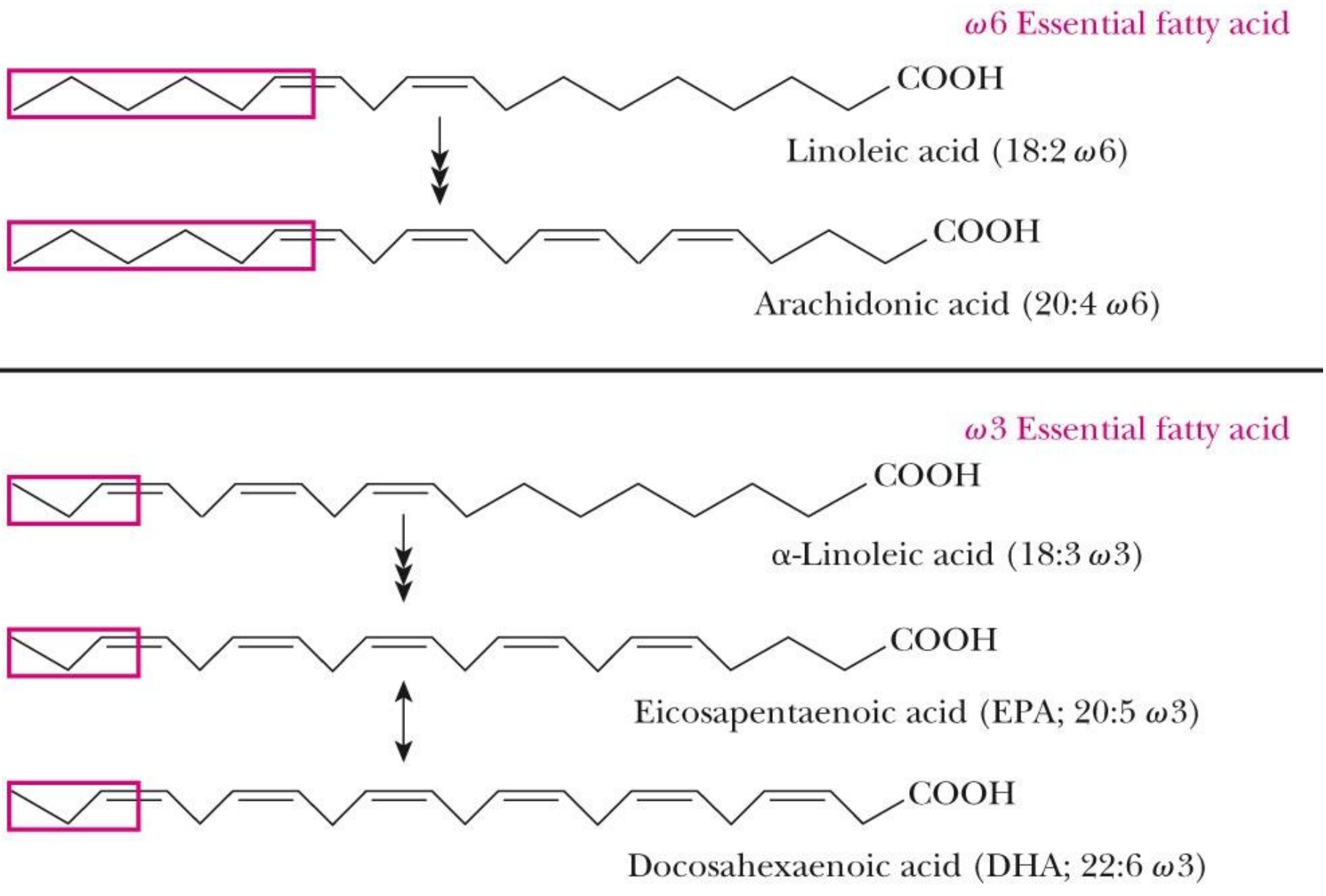
ω3 and ω6 – Essential Fatty Acids with Many Functions



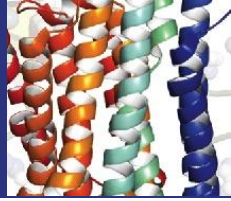
- Linoleic acid and linolenic acid are termed *essential fatty acids* because animals cannot synthesize them and must acquire them in their diet
- Linoleic acid is the precursor of arachidonic acid and both these are termed **ω6 fatty acids**
- Linolenic acid is the precursor of eicosapentaenoic acid and docosahexaenoic acid and these three are termed **ω3 fatty acids**
- ω3 fatty acids are cardioprotective, anti-inflammatory, and anticarcinogenic
- ω6 fatty acids are precursors of prostaglandins, thromboxanes, and leukotrienes (See Section 24.3)

ω3 and ω6 – Essential Fatty Acids with Many Functions





Regulation of FA Synthesis



- Regulatory control of fatty acid metabolism is an interplay of allosteric modifiers, phosphorylation and dephosphorylation cycles and hormones
- **Malonyl-CoA** blocks the carnitine acyltransferase and thus inhibits beta-oxidation
- **Citrate** activates acetyl-CoA carboxylase
- **Fatty acyl-CoAs** inhibit acetyl-CoA carboxylase
- Hormones regulate ACC
- **Glucagon** activates lipases/inhibits ACC
- **Insulin** inhibits lipases/activates ACC

Regulation of FA Synthesis

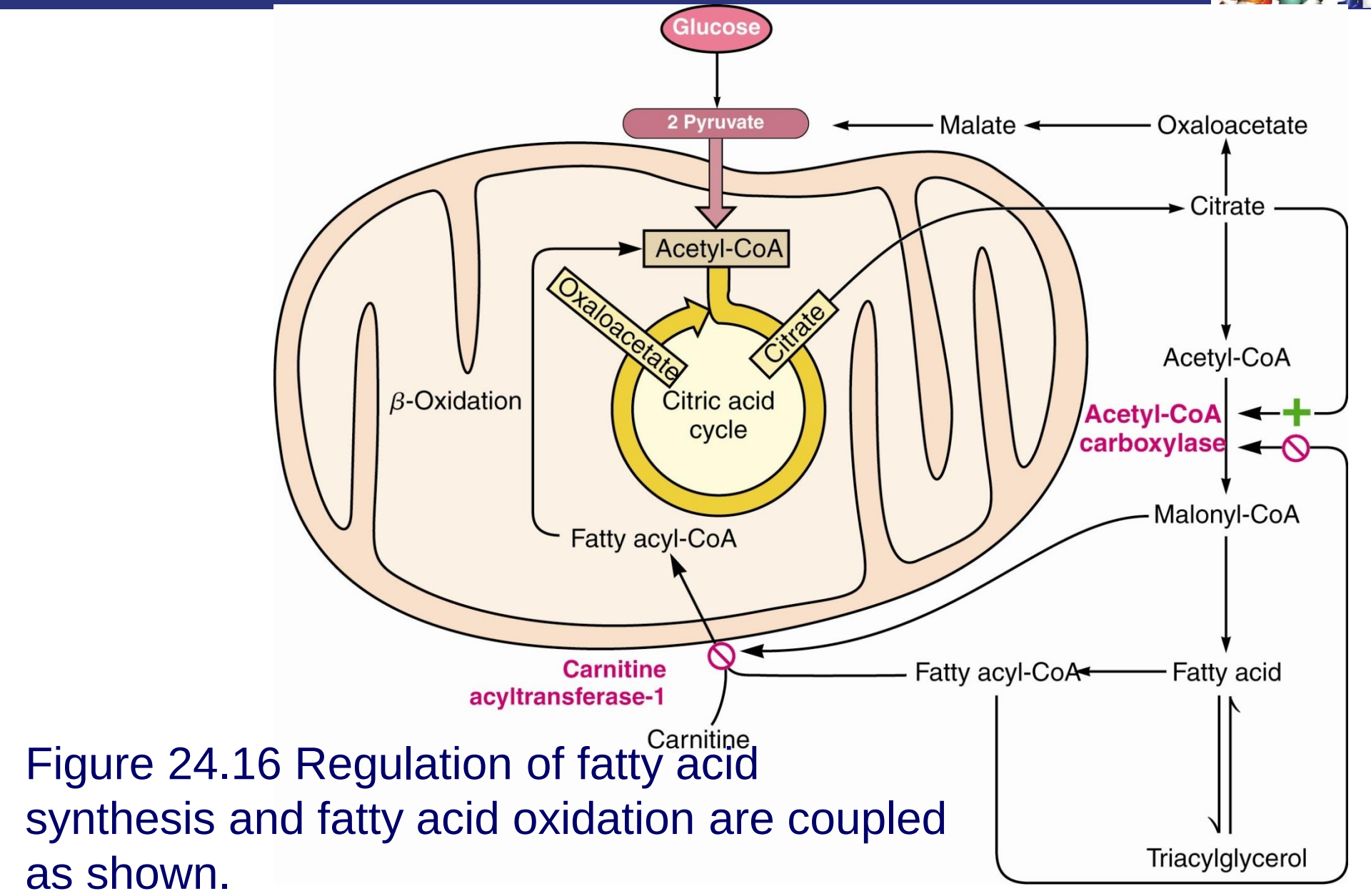
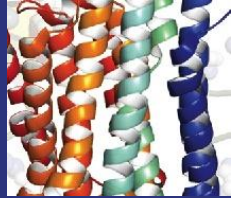


Figure 24.16 Regulation of fatty acid synthesis and fatty acid oxidation are coupled as shown.



Hormonal Signals Regulate ACC and Fatty Acid Biosynthesis

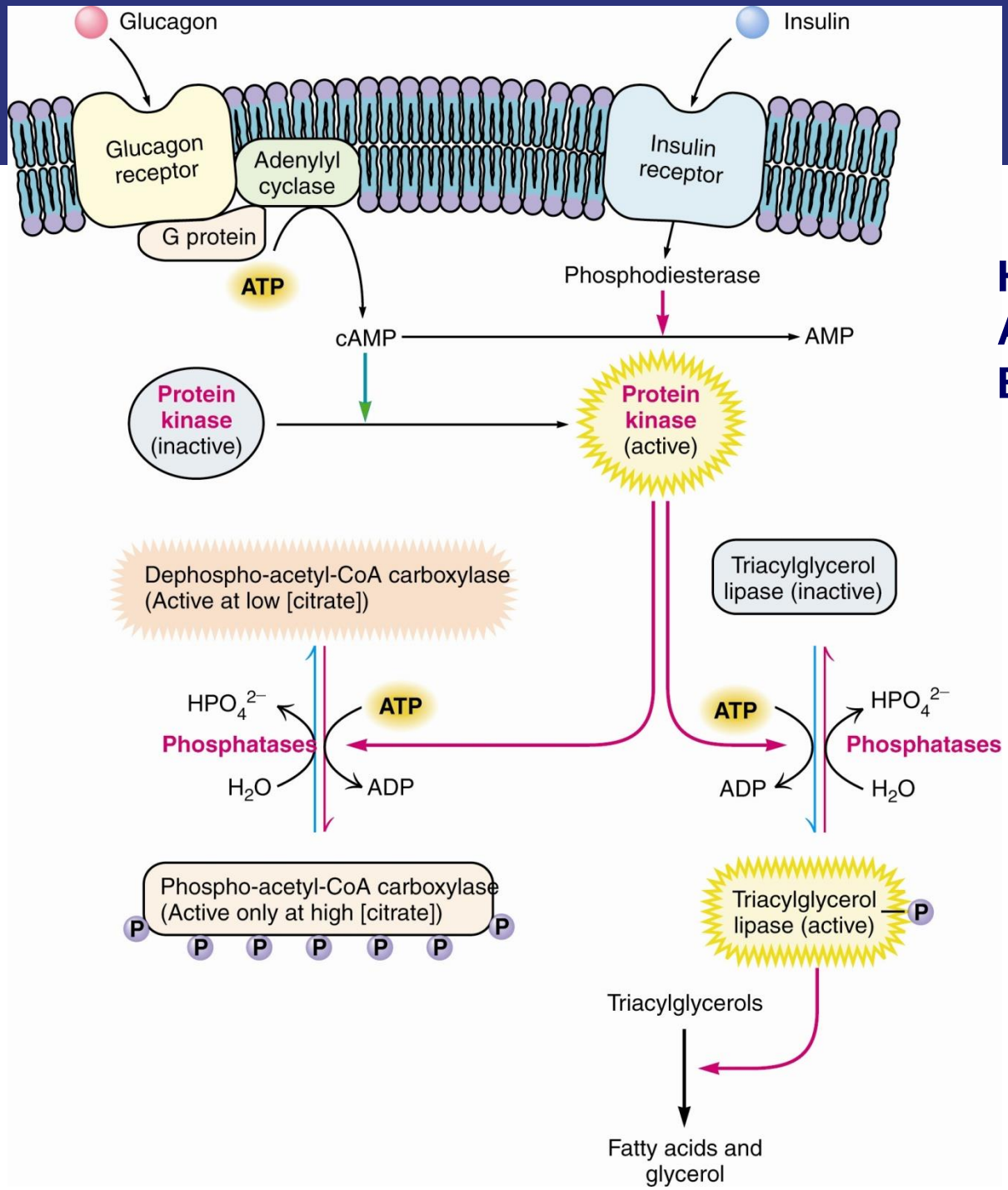
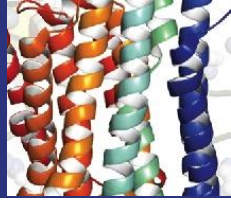


Figure 24.17 Hormonal signals regulate fatty acid synthesis, primarily through actions on acetyl-CoA carboxylase, with additional effects on triacylglycerol lipase.

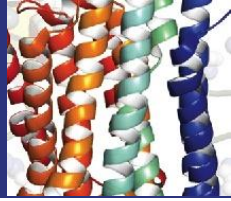
24.2 How Are Complex Lipids Synthesized?



Synthetic pathways depend on organism

- Sphingolipids and triacylglycerols only made in eukaryotes
- PE accounts for 75% of PLs in *E.coli*
- No PC, PI, sphingolipids, cholesterol in *E.coli*
- But some bacteria do produce PC

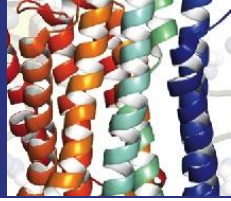
Glycerolipid Biosynthesis



CTP drives formation of CDP complexes

- Phosphatidic acid is the precursor for all other glycerolipids in eukaryotes
- See Figure 24.18
- PA is made either into DAG or CDP-DAG
- Note the roles of **CDP-choline** and **CDP-ethanolamine** in synthesis of PC and PE in Figure 24.19
- Note exchange of **ethanolamine** for **serine** (Figure 24.21)

Glycerolipids are Synthesized by Phosphorylation and Acylation of Glycerol



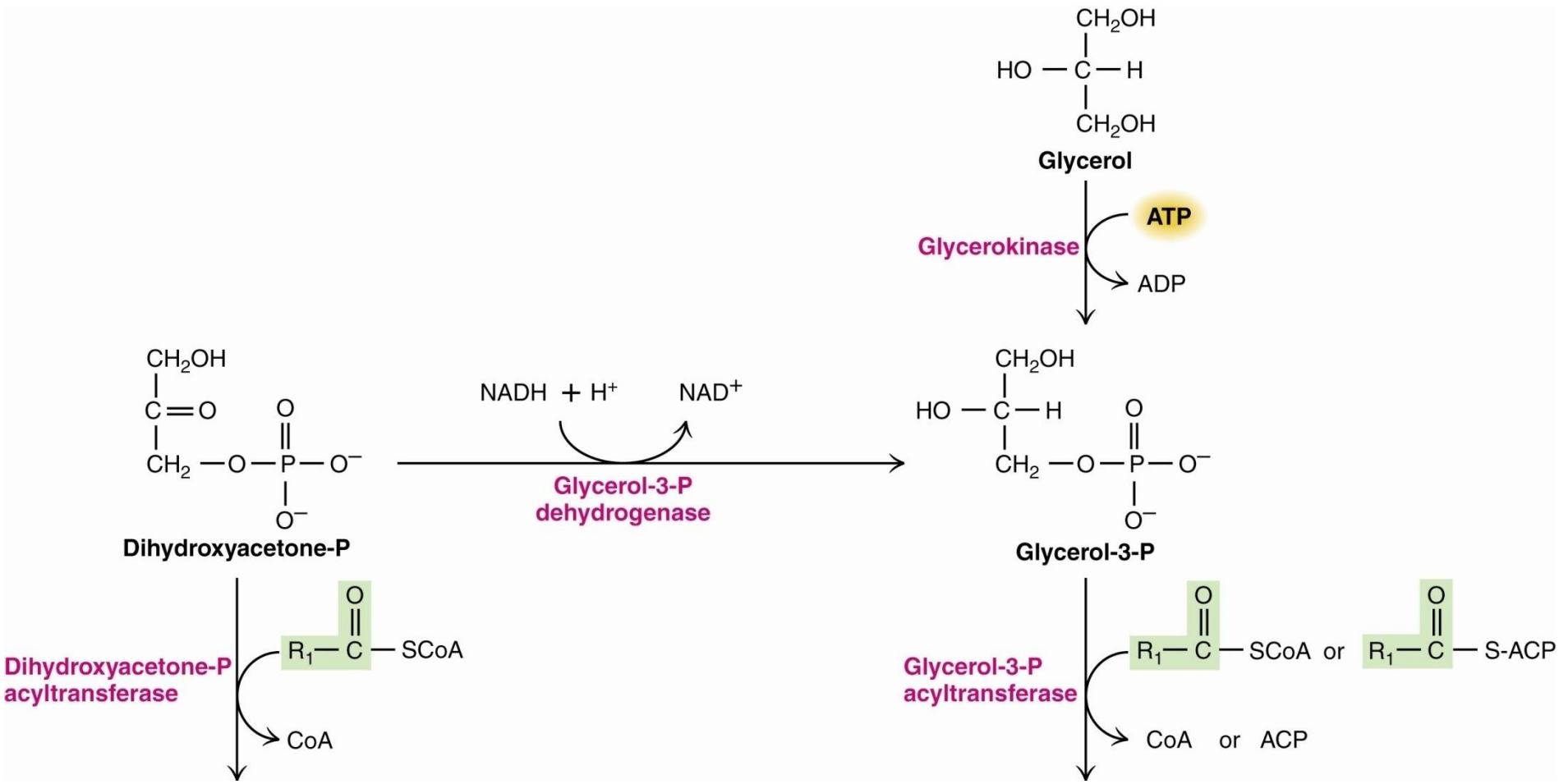
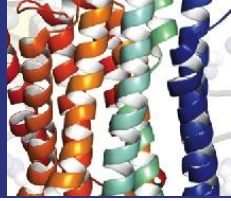


Figure 24.18 Synthesis of glycerolipids in eukaryotes begins with the formation of phosphatidic acid, which may be formed from dihydroxyacetone phosphate or glycerol.

Glycerolipids are Synthesized by Phosphorylation and Acylation of Glycerol



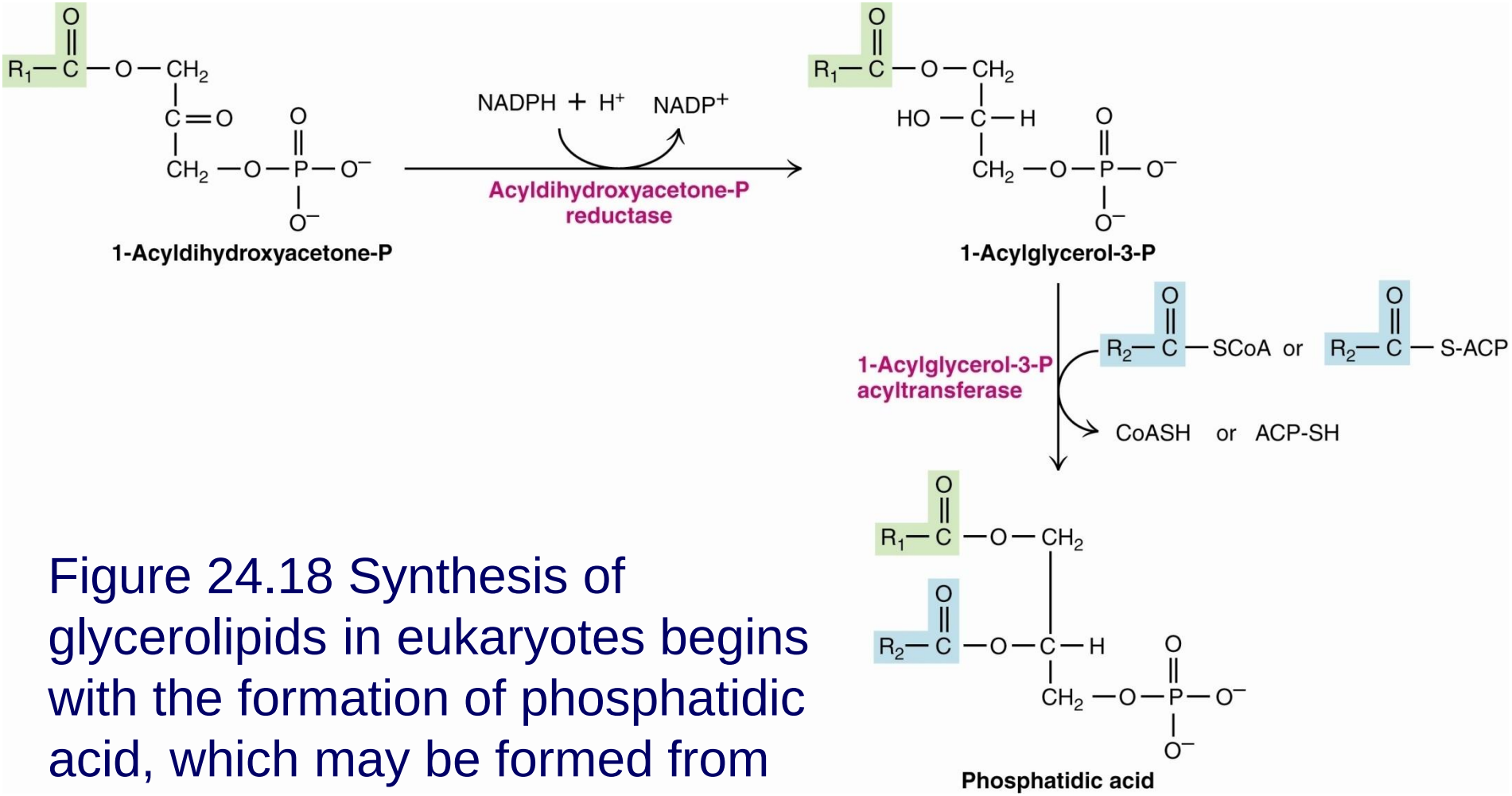


Figure 24.18 Synthesis of glycerolipids in eukaryotes begins with the formation of phosphatidic acid, which may be formed from dihydroxyacetone phosphate or glycerol.

Eukaryotes Synthesize Glycerolipids From CDP-Diacylglycerol or Diacyglycerol

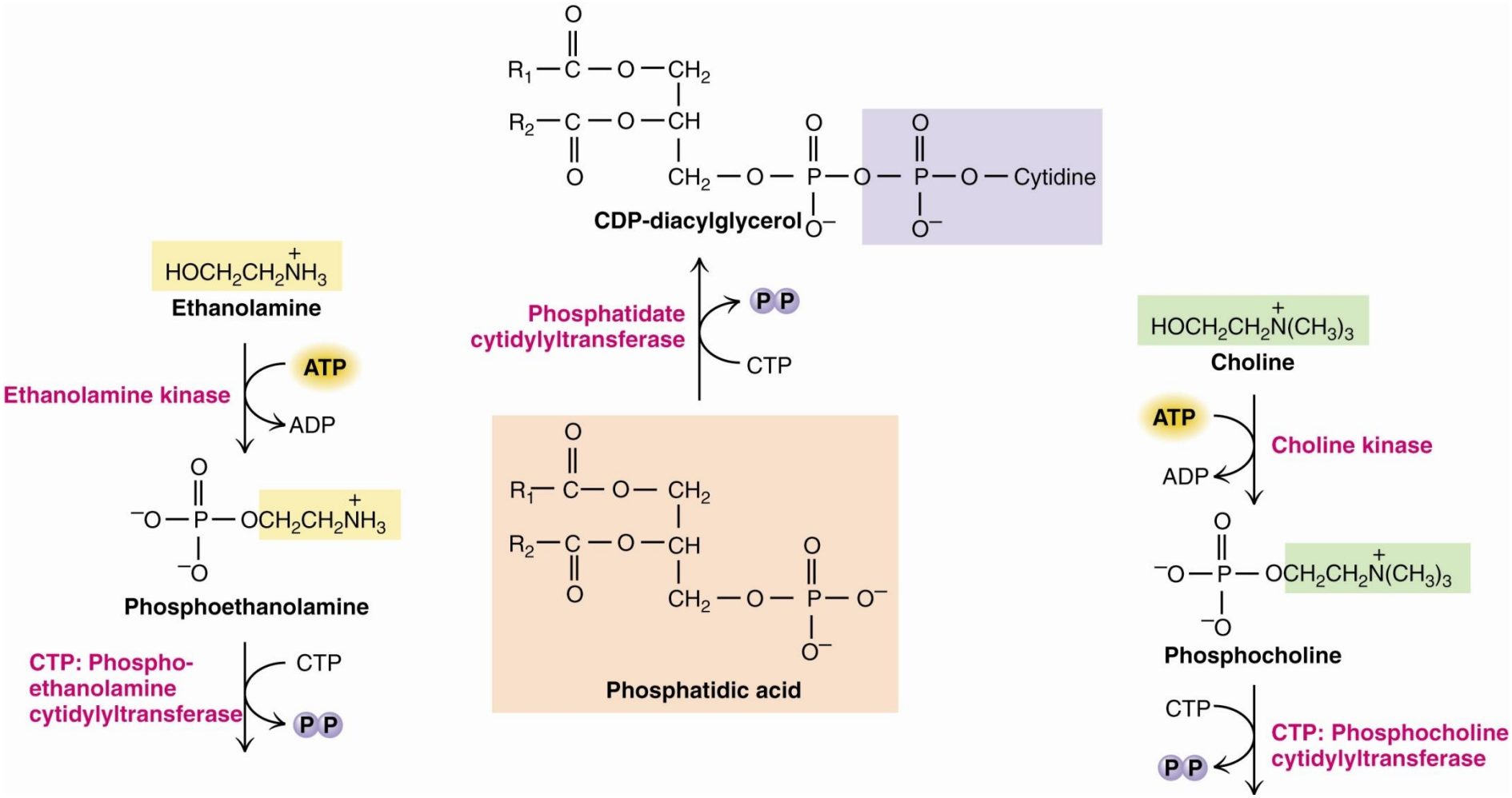
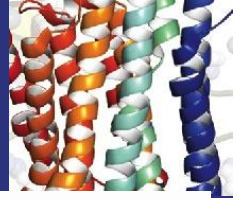


Figure 24.19 Diacylglycerol and CDP-diacylglycerol are the principal precursors of glycerolipids in eukaryotes.

Eukaryotes Synthesize Glycerolipids From CDP-Diacylglycerol or Diacyglycerol



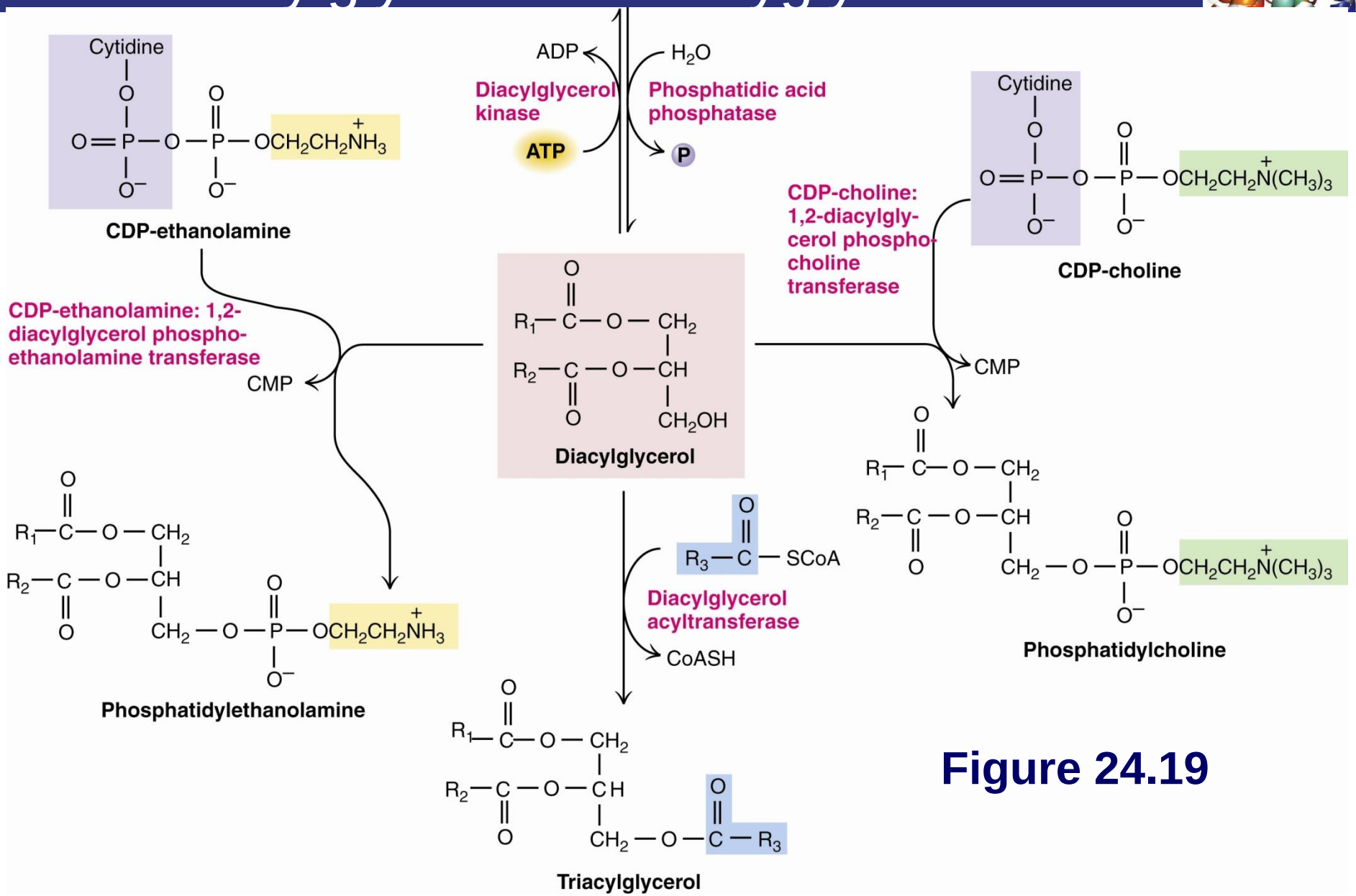
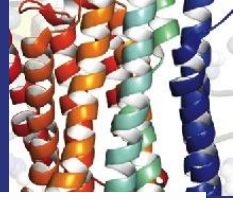


Figure 24.19

Monoacylglycerol and Diacylglycerol Are Precursors for Synthesis of Triacylglycerols



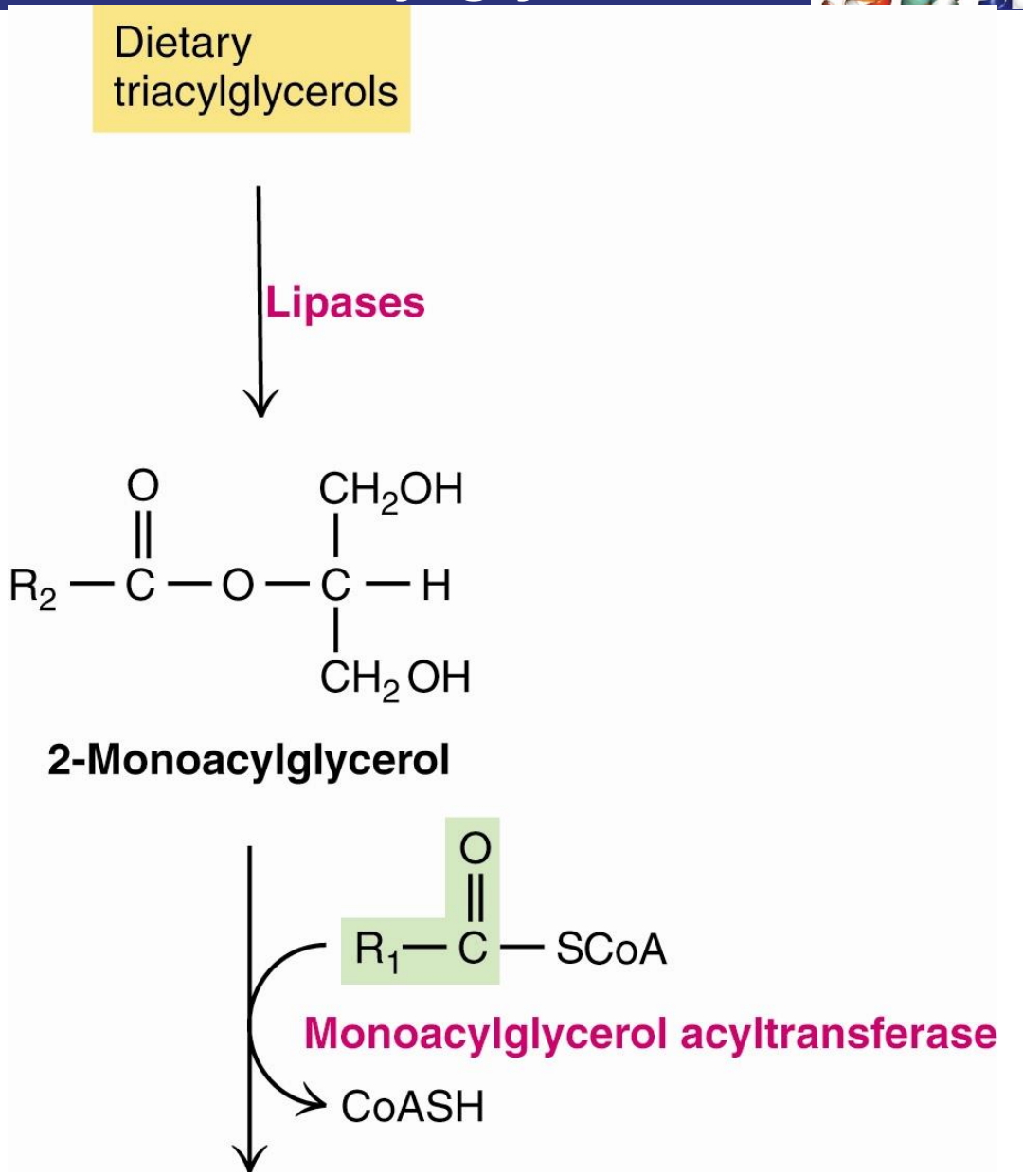
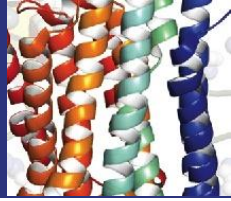


Figure 24.20 Triacylglycerols are formed primarily by the action of **acyltransferases** on monoacylglycerol and diacylglycerol.



Monoacylglycerol and Diacylglycerol Are Precursors for Synthesis of Triacylglycerols

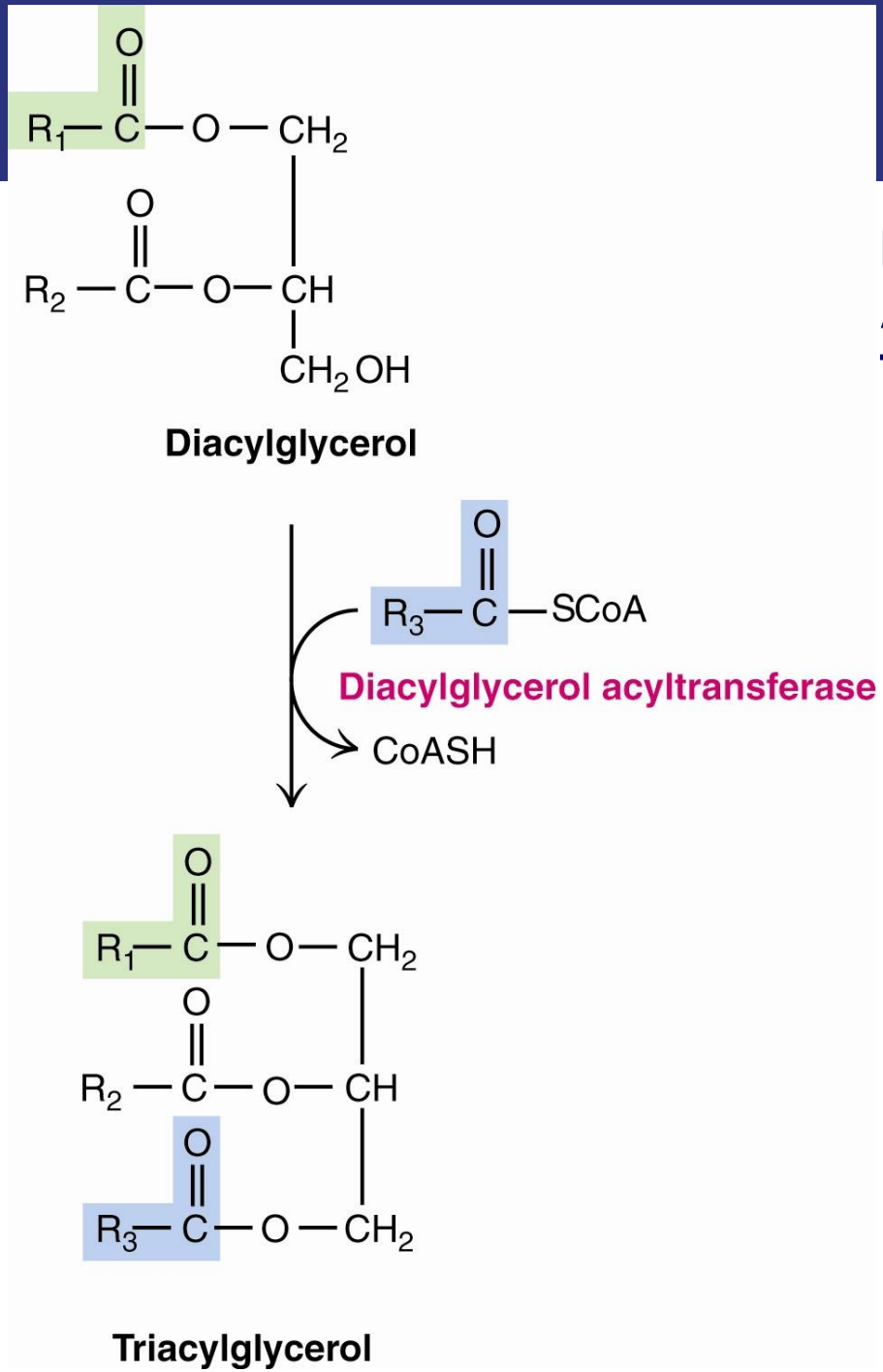


Figure 24.20 Triacylglycerols are formed primarily by the action of **acyltransferases** on monoacylglycerol and diacylglycerol.

Exchange of Ethanolamine for Serine Converts Phosphatidylethanolamine to Phosphatidylserine

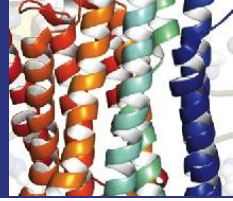
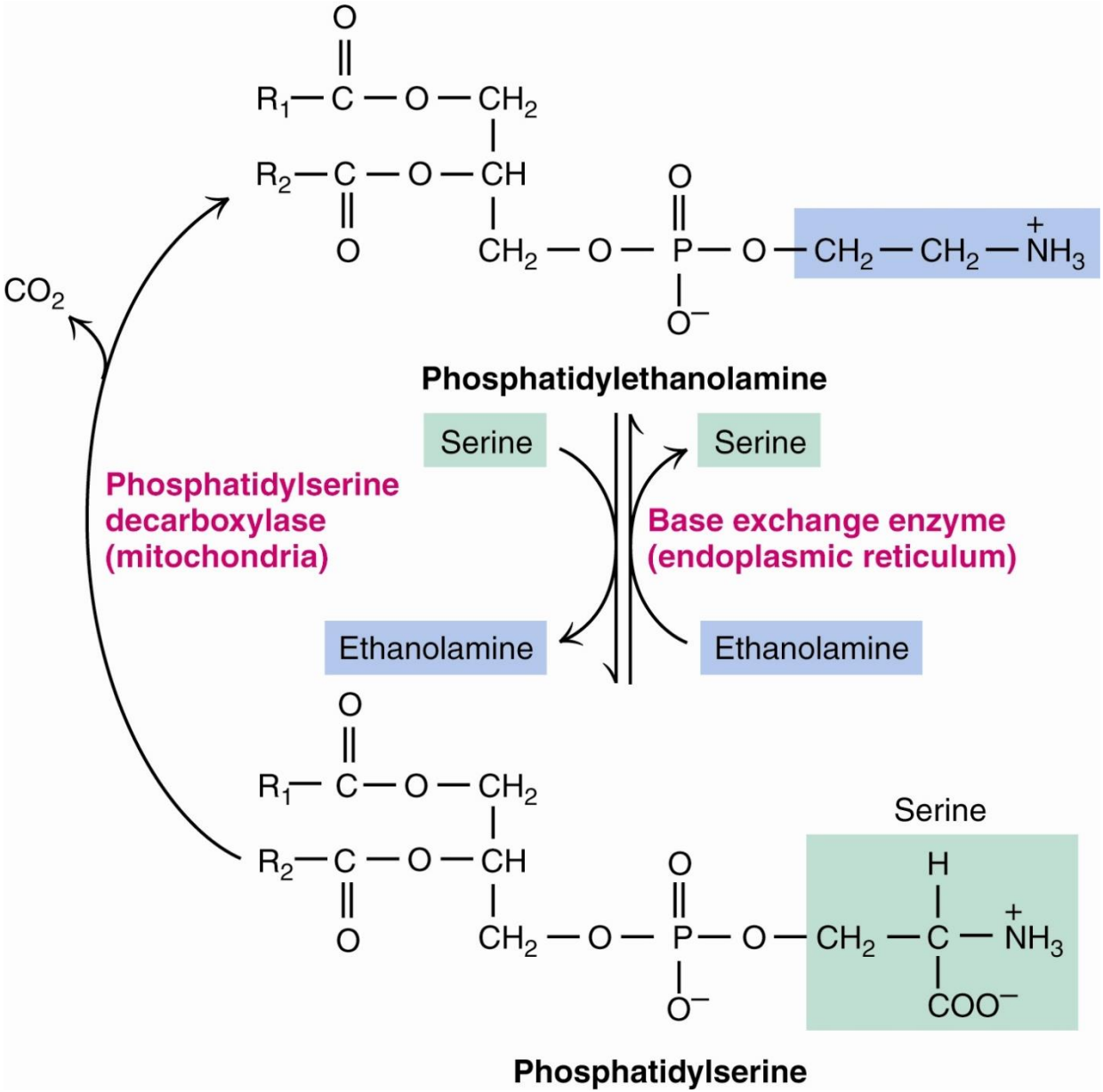


Figure 24.21 The interconversion of phosphatidylethanolamine and phosphatidylserine in mammals.



Eukaryotes Synthesize Other Phospholipids from CDP-Diacylglycerol

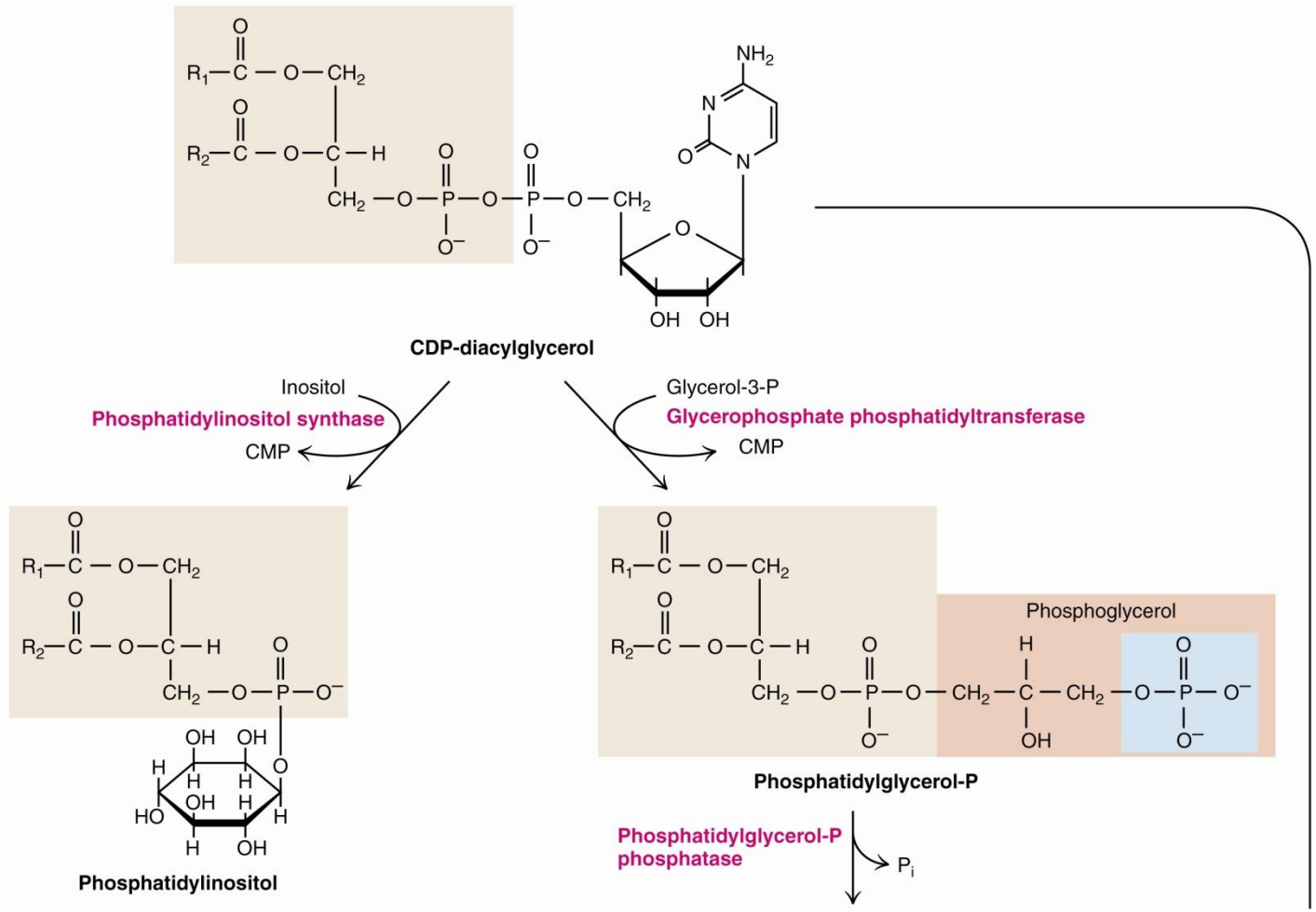
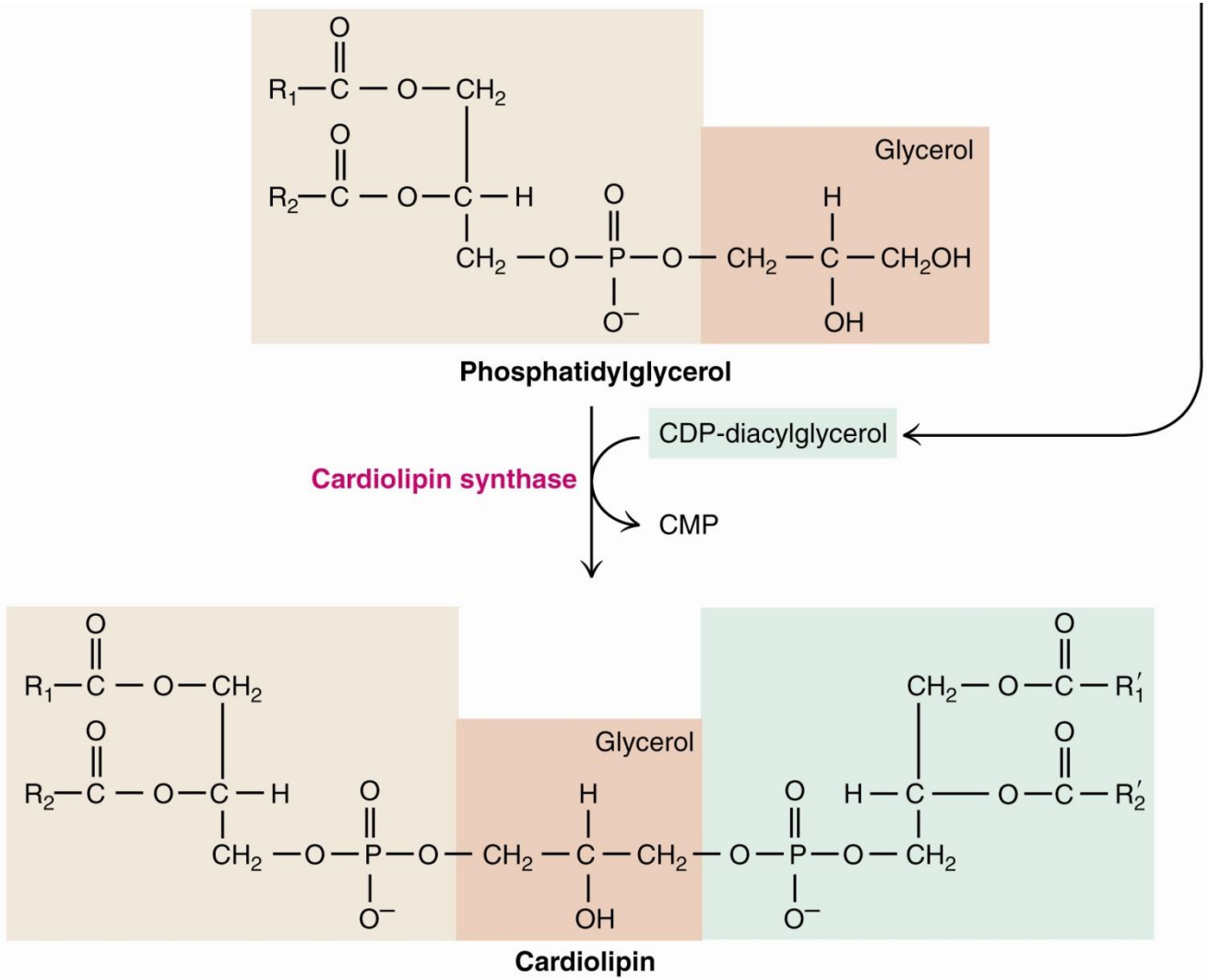


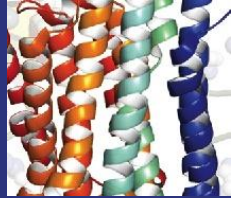
Figure 24.22 **CDP-Diacylglycerol** is a precursor of phosphatidylinositol, phosphatidylglycerol, and cardiolipin in eukaryotes.

Eukaryotes Synthesize Other Phospholipids from CDP-Diacylglycerol

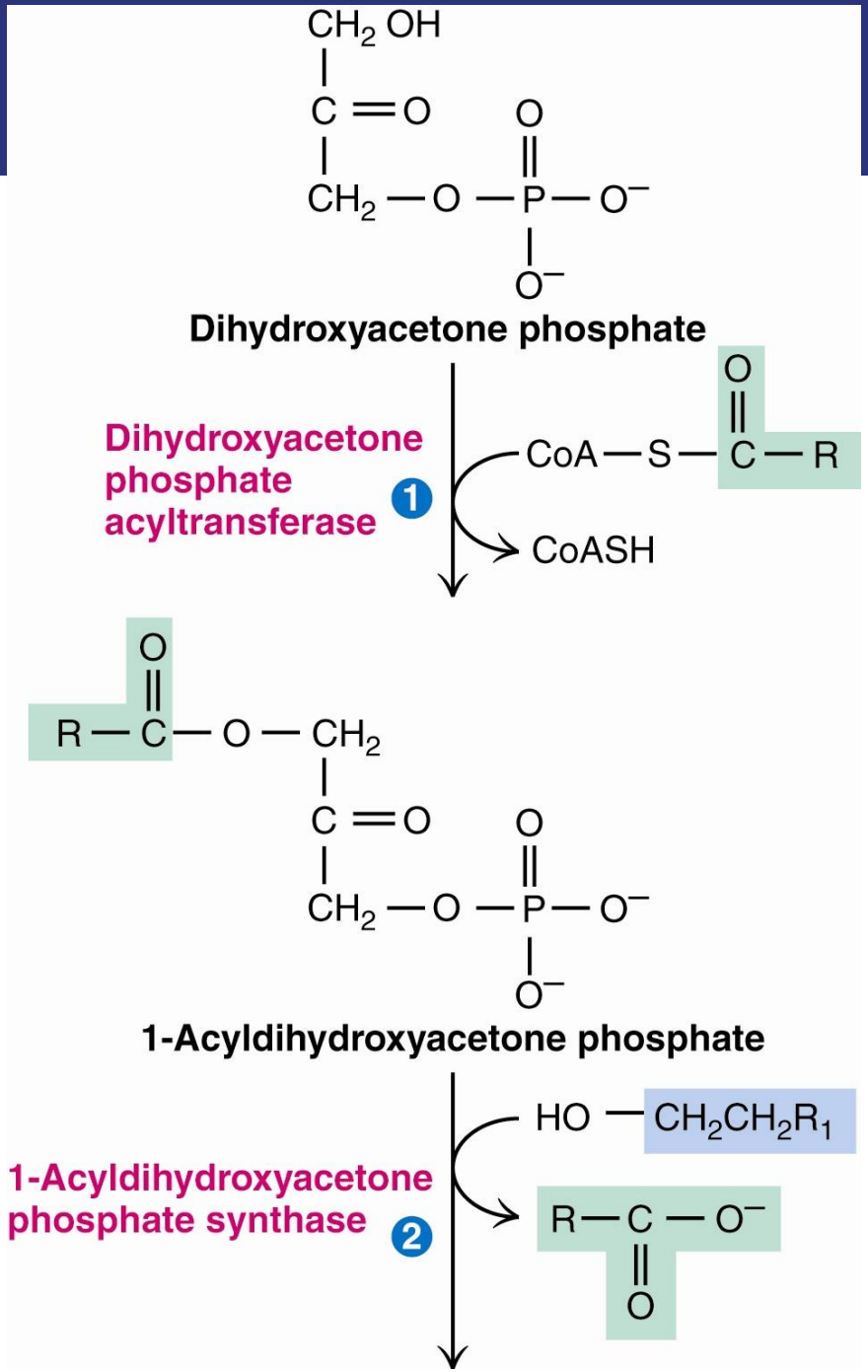
Figure 24.22 **CDP-Diacylglycerol** is a precursor of phosphatidylinositol, phosphatidylglycerol, and cardiolipin in eukaryotes.



Dihydroxyacetone Phosphate is a Precursor to the Plasmalogens



- Acylation activates and an exchange reaction produces the ether linkage
- Ketone reduction is followed by acylation
- **CDP-ethanolamine** delivers the head group
- A **desaturase** produces the double bond in the alkyl chain



Dihydroxyacetone Phosphate is a Precursor to the Plasmalogens

Figure 24.23 Biosynthesis of plasmalogens in animals.

Dihydroxyacetone Phosphate is a Precursor to the Plasmalogens

Figure 24.23 Biosynthesis of plasmalogens in animals.

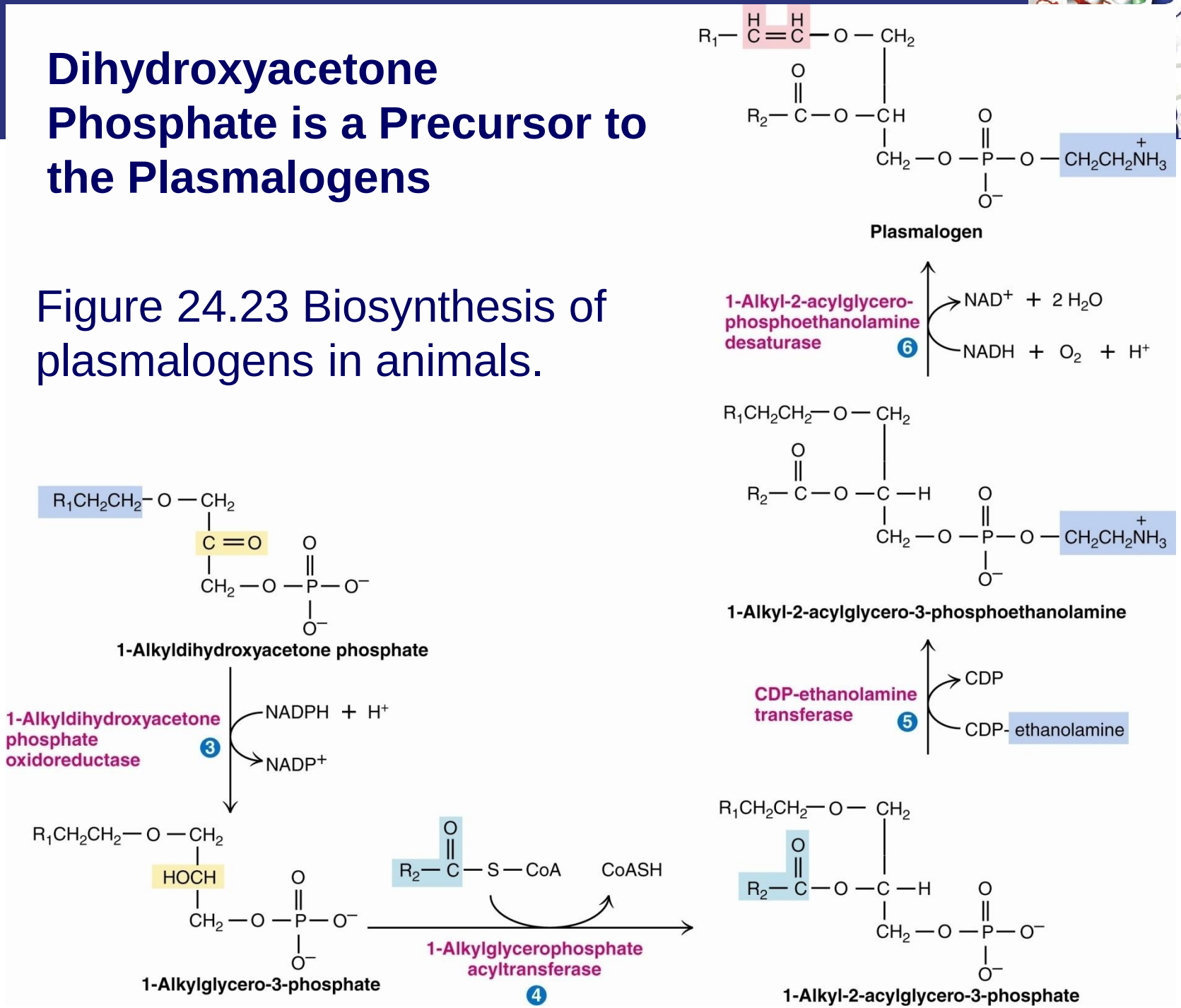
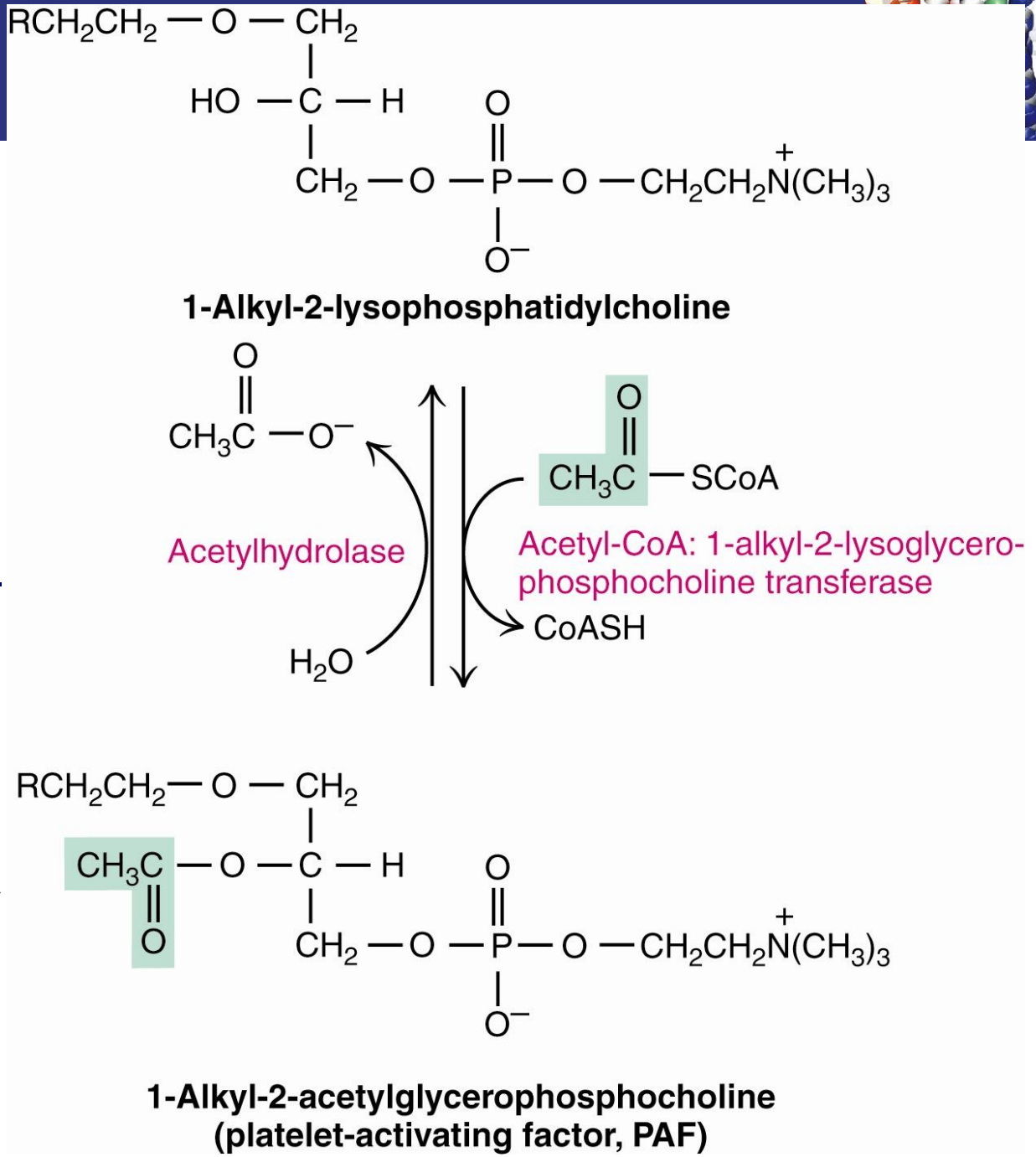
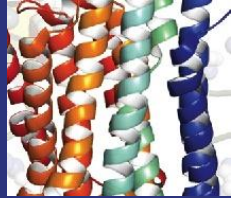


Figure 24.24 Platelet-activating factor is formed by acetylation of 1-alkyl-2-lysophosphatidyl-choline.

Platelet-activating factor is degraded by the action of **acetylhydrolase**.



Sphingolipid Biosynthesis Begins with Condensation of Serine and Palmitoyl-CoA



High levels made in neural tissue

- Initial reaction is a condensation of **serine** and **palmitoyl-CoA**
- **3-ketosphinganine synthase** requires **pyridoxal phosphate (PLP)** as a coenzyme
- Ketone is reduced with help of NADPH
- Acylation is followed by double bond formation
- See Figure 24.25
- Resulting **ceramide** is precursor for other sphingolipids

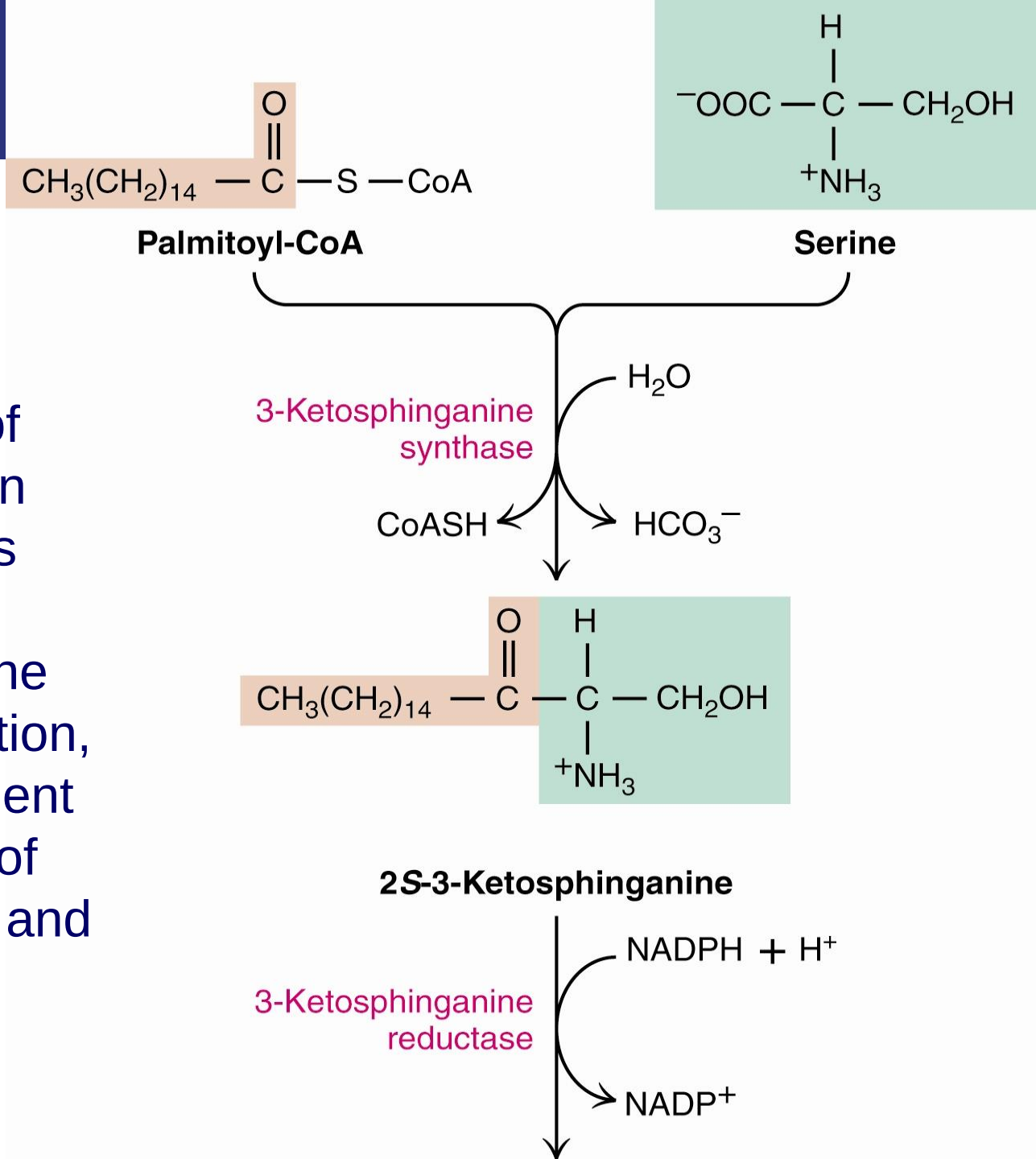
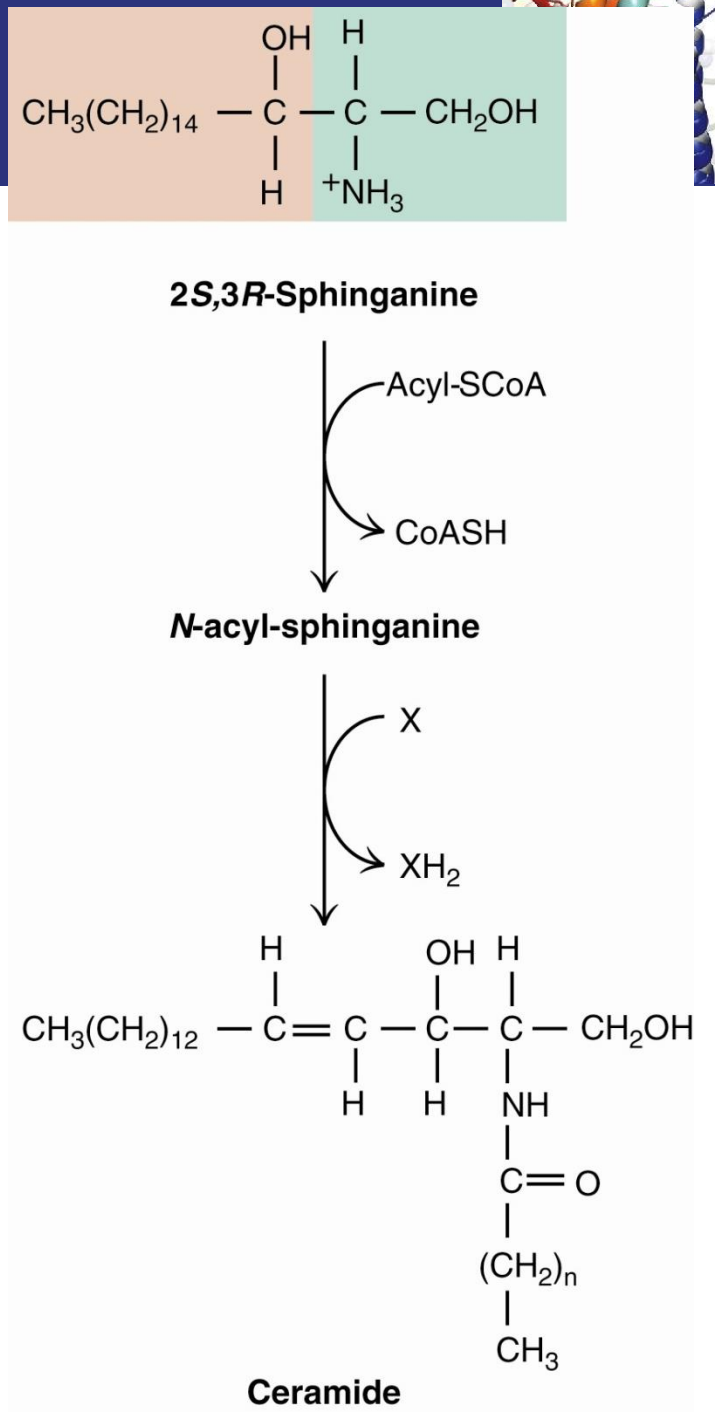


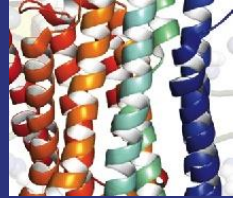
Figure 24.25 Biosynthesis of sphingolipids in animals begins with the 3-ketosphinganine synthase reaction, a PLP-dependent condensation of palmitoyl-CoA and serine.

Sphingolipid Biosynthesis Begins With Condensation of Serine and Palmitoyl-CoA

Figure 24.25 Biosynthesis of sphingolipids in animals begins with the 3-ketosphinganine synthase reaction, a PLP-dependent condensation of palmitoyl-CoA and serine. Subsequent reduction of the keto group, acylation, and desaturation (via reduction of an electron acceptor, X) form ceramide, the precursor of other sphingolipids.



Ceramide is the Precursor for Other Sphingolipids and Cerebrosides



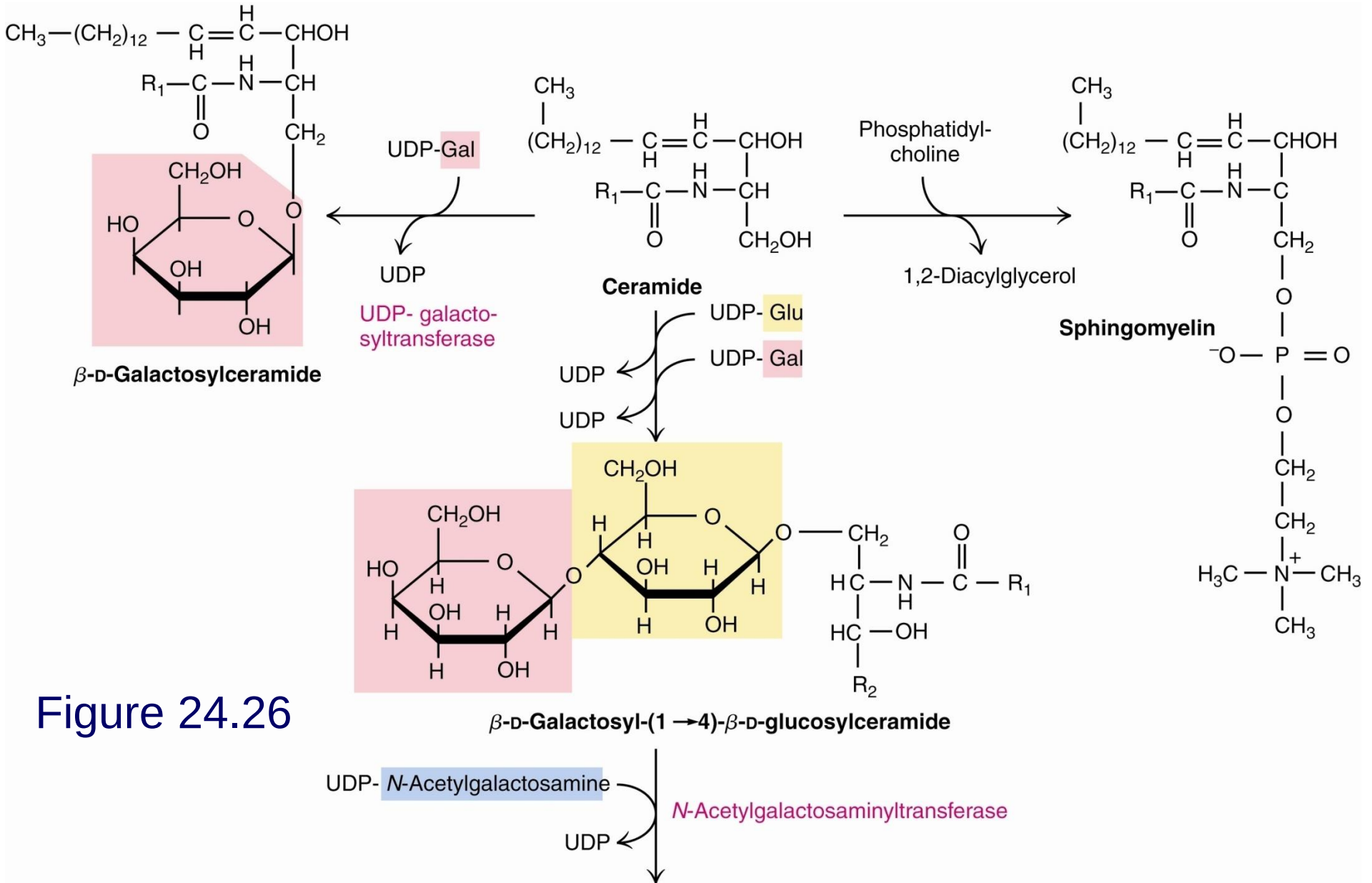
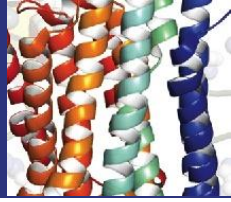


Figure 24.26



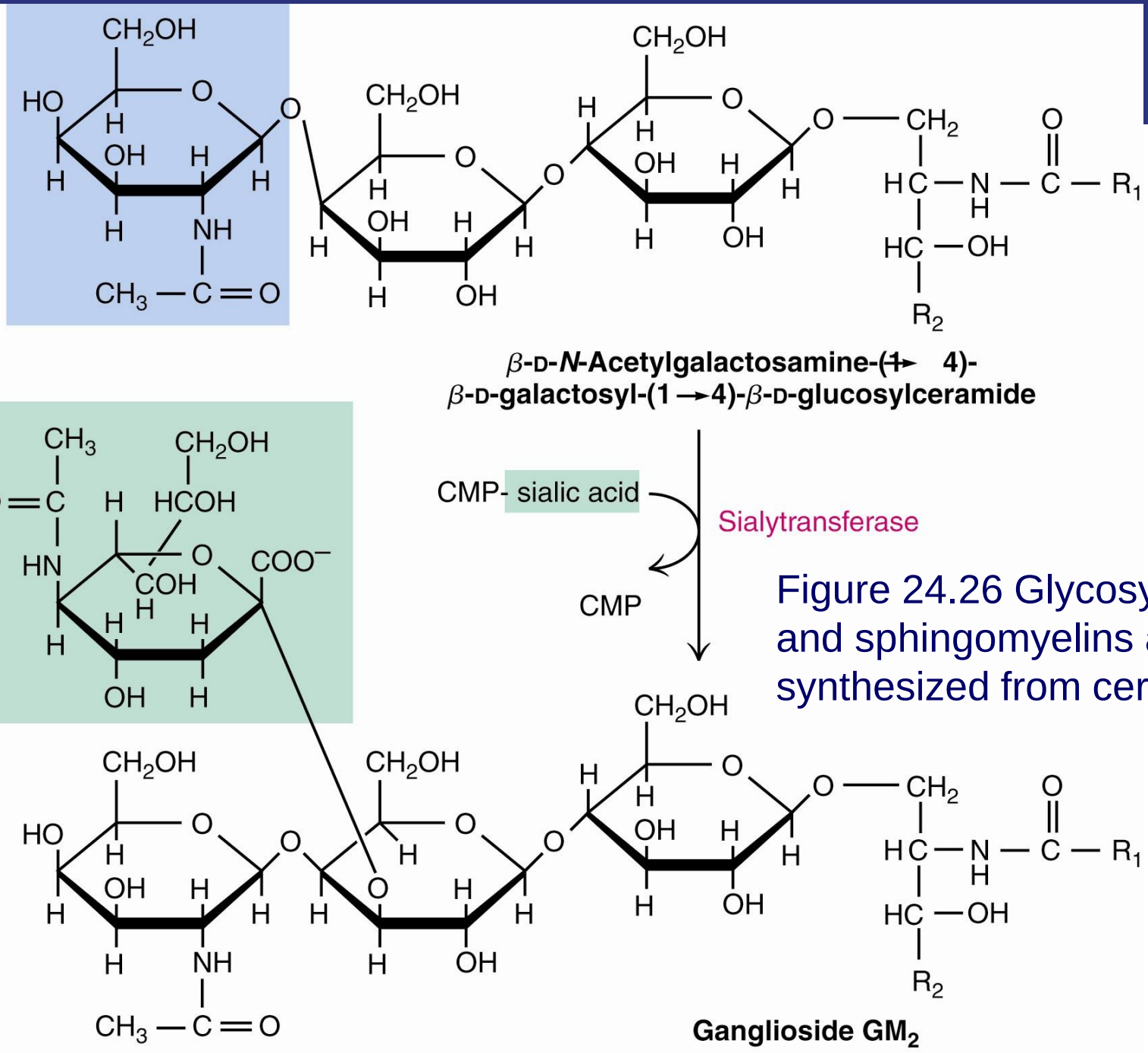
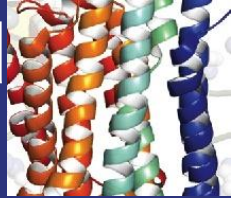


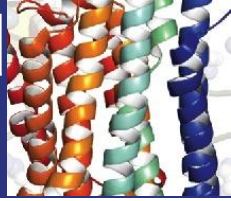
Figure 24.26 Glycosylceramides and sphingomyelins are synthesized from ceramide.

24.3 How Are Eicosanoids Synthesized, and What Are Their Functions?



- Eicosanoids (i.e., "20-carbon" molecules) are ubiquitous breakdown products of phospholipids
- Under certain stimuli, cells activate the breakdown of selected lipids to release arachidonic acid, the precursor of the eicosanoids
- Eicosanoids are local hormones
  - Prostaglandins
  - Thromboxanes
  - Leukotrienes
  - Other hydroxyeicosanoic acids

24.3 How Are Eicosanoids Synthesized, and What Are Their Functions?



- Prostaglandins are formed from arachidonate by oxidation and cyclization
- Biosynthesis is initiated by an enzyme from the endoplasmic reticulum, **prostaglandin endoperoxide H synthase (PGHS)**
- Also known as **cycloxygenase (COX)**
- The enzyme has two different activities:
  - Cyclooxygenase (COX)
  - Peroxidase (POX)
- See Figure 24.28

24.3 How Are Eicosanoids Synthesized, and What Are Their Functions?

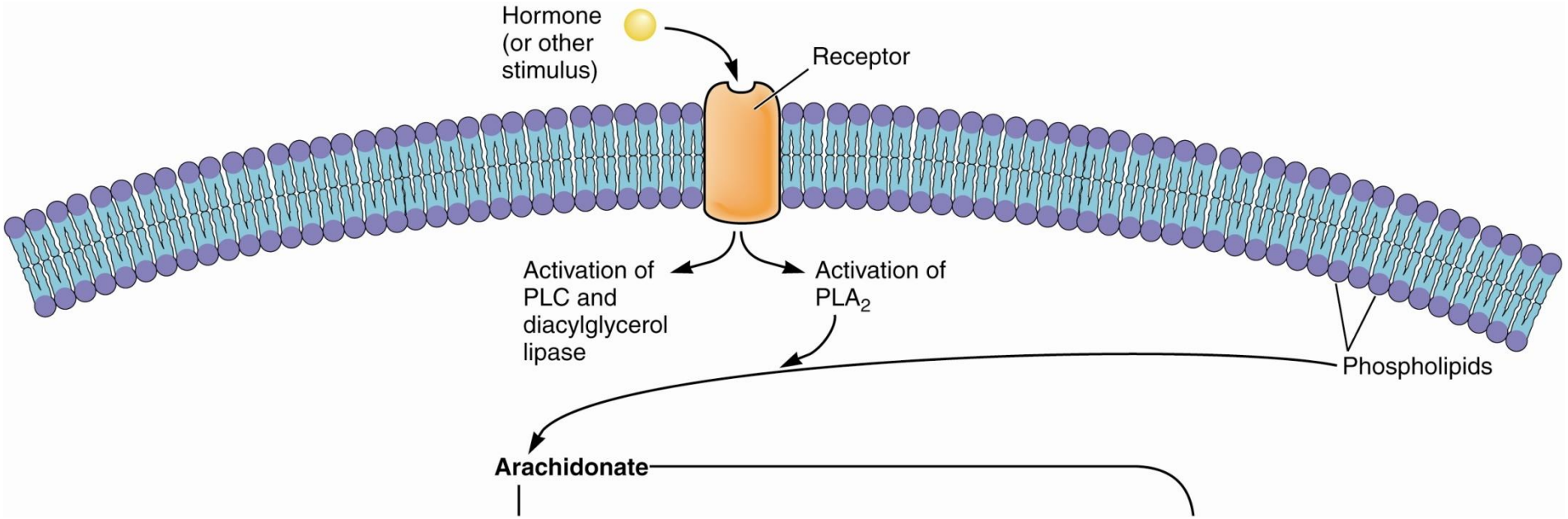
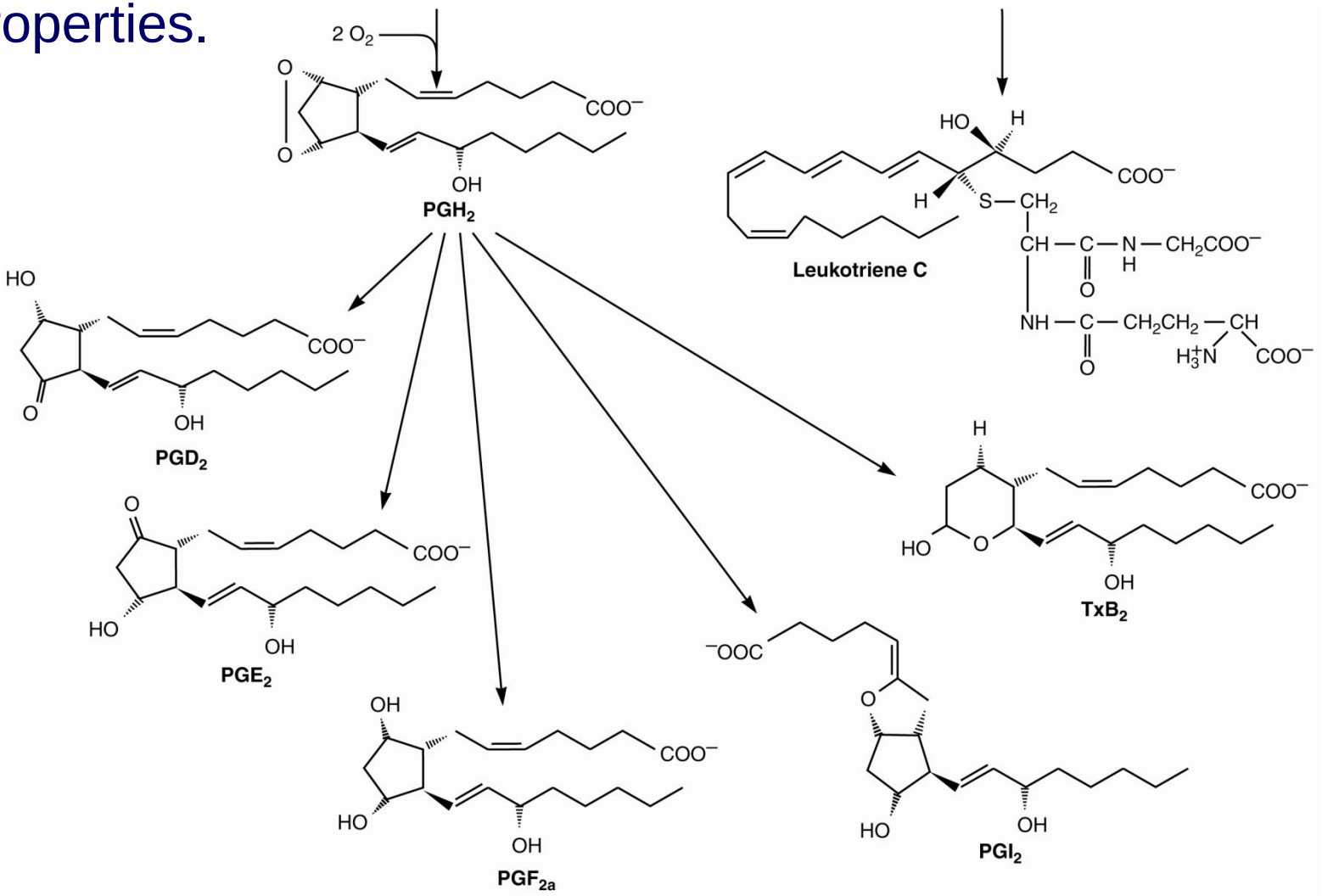


Figure 24.27 Arachidonic acid, derived from breakdown of phospholipids (PL), is the precursor of prostaglandins, thromboxanes, and leukotrienes.

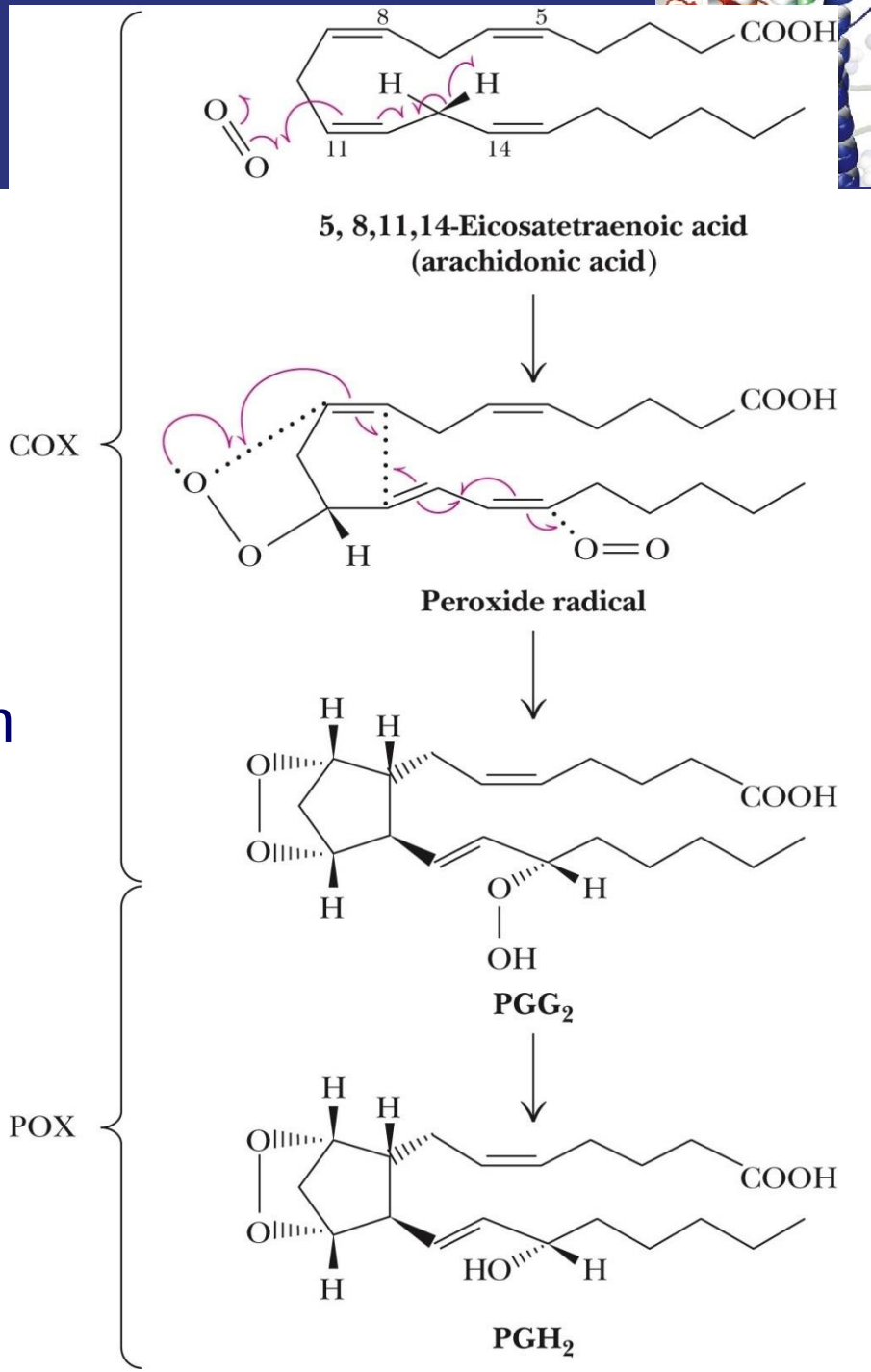
24.3 How Are Eicosanoids Synthesized, and What Are Their Functions?

Figure 24.27 The letters used to name the prostaglandins are assigned on the basis of similarities in structure and physical properties.

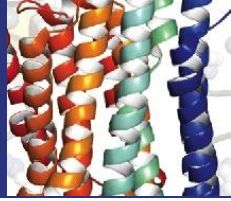


Prostaglandin endoperoxide H synthase

Figure 24.28 Prostaglandin endoperoxide H synthase possesses two activities: cyclooxygenase (COX) and a glutathione-dependent peroxidase (POX). The mechanism of the reaction begins with hydrogen atom abstraction by a tyrosine radical on the enzyme, followed by rearrangement to cyclize and incorporate two oxygen molecules. Reduction of the peroxide at C-15 completes the reaction. COX is the site of action of aspirin and other analgesic agents.



Aspirin and Other NSAIDs Block Synthesis of Prostaglandins



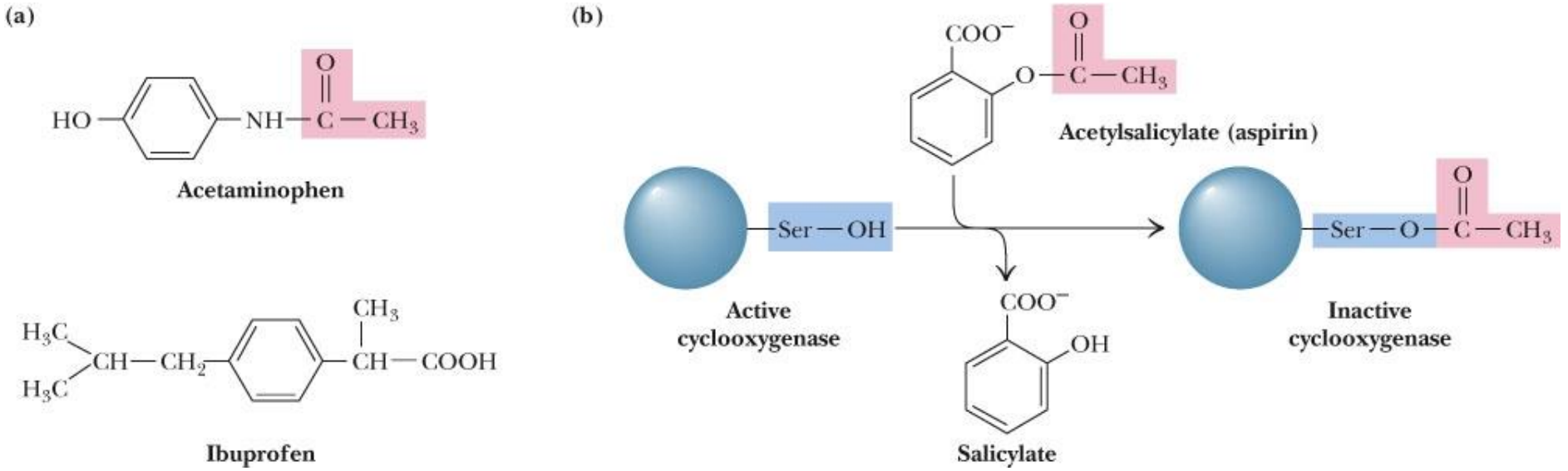
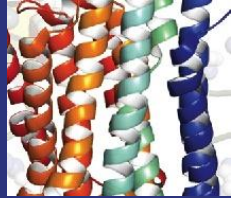


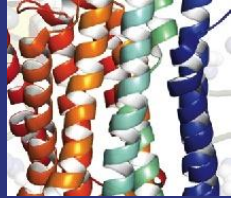
Figure 24.29 (a) The structures of several common analgesic agents. Acetaminophen is marketed under the trade name Tylenol. Ibuprofen is sold as Motrin, Nuprin, and Advil. (b) Acetylsalicylate (aspirin) inhibits the COX activity of endoperoxide synthase via acetylation (covalent modification) of Ser-530.

The Molecular Basis for the Action of Nonsteroidal Anti-Inflammatory Drugs

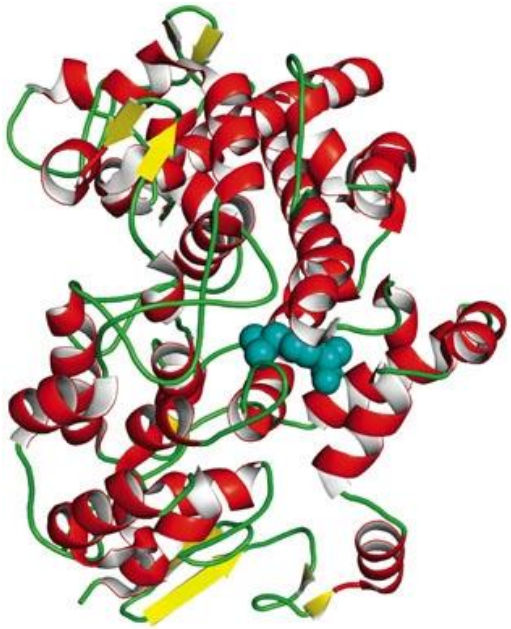


- Prostaglandins are potent mediators of inflammation
- The first steps in conversion of arachidonic acid to prostaglandins are catalyzed by PGHS or COX
- This enzyme is inhibited by the nonsteroidal anti-inflammatory drugs (NSAIDs)
- Animals possess two forms: COX-1 and COX-2
- The “COX-2 inhibitors” (e.g., Celebrex) bind to COX-2 but not COX-1
- Because COX-1 has a bulkier isoleucine at position 523 which prevents binding of NSAIDs
- At the same position, COX-2 has valine, which accommodates the NSAIDs

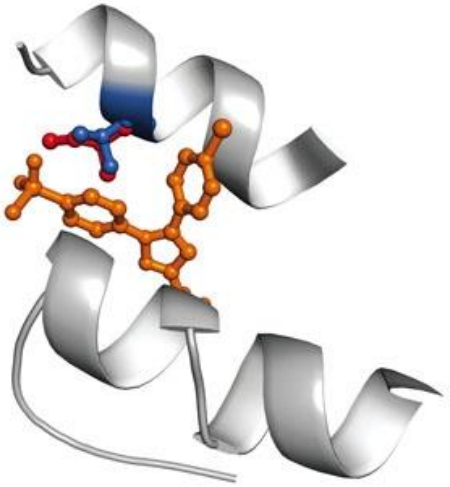
The Molecular Basis for the Action of Nonsteroidal Anti-Inflammatory Drugs



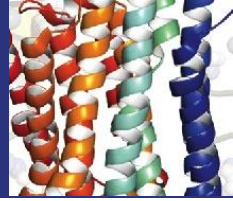
The structure of COX-1, showing residues 33 to 583.

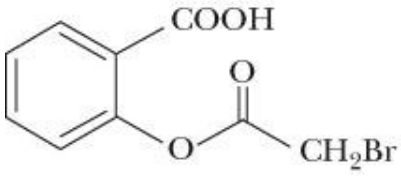


A superposition of COX-1 and COX-2. COX-2 has Val (blue) at position 523, whereas COX-1 has Ile (red).

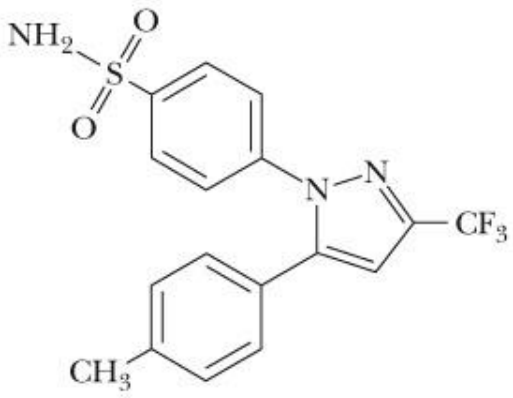


The Molecular Basis for the Action of Nonsteroidal Anti-Inflammatory Drugs

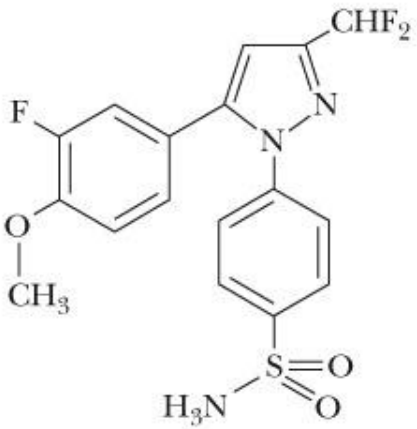




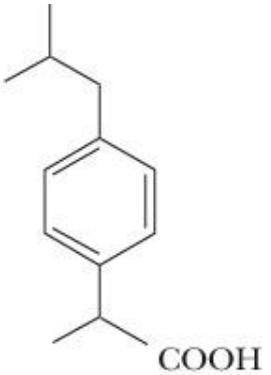
Bromoaspirin



Celebrex



Deramaxx for dogs*

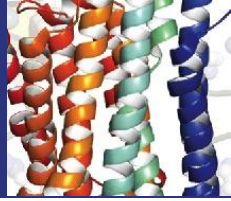


Ibuprofen

* Abby Garrett took this.

Structures of several NSAIDs. Aspirin and bromoaspirin bind covalently to COX-1 and COX-2. Ibuprofen binds noncovalently to both. Celebrex and Deramaxx bind selectively to COX-2.

24.4 How Is Cholesterol Synthesized?



- **Cholesterol** is the most prevalent steroid in animals
- Plants do not contain cholesterol, but they DO contain steroids very similar in structure (see page 236 of the text)
- Cholesterol is a crucial component of cell membranes and is a precursor to all bile acids and all steroid hormones
- Also, vitamin D is derived from a precursor of cholesterol
- Liver is the primary site of cholesterol synthesis
- The cholesterol biosynthetic pathway begins with synthesis of **mevalonate**

24.4 How Is Cholesterol Synthesized?

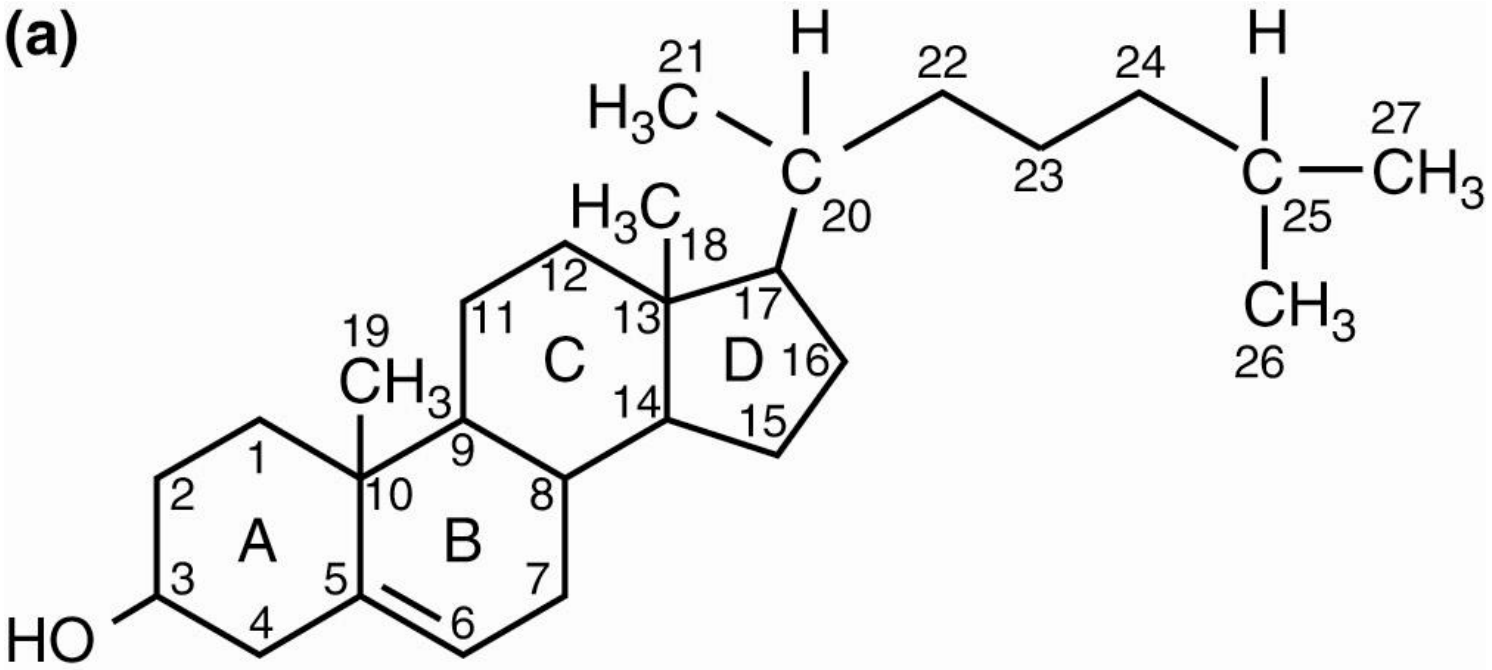
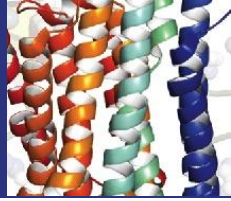


Figure 24.30 The structure of cholesterol, drawn (a) in the traditional planar motif and (b) in a form that more accurately describes the conformation of the ring system.

24.4 – How Is Cholesterol Synthesized?

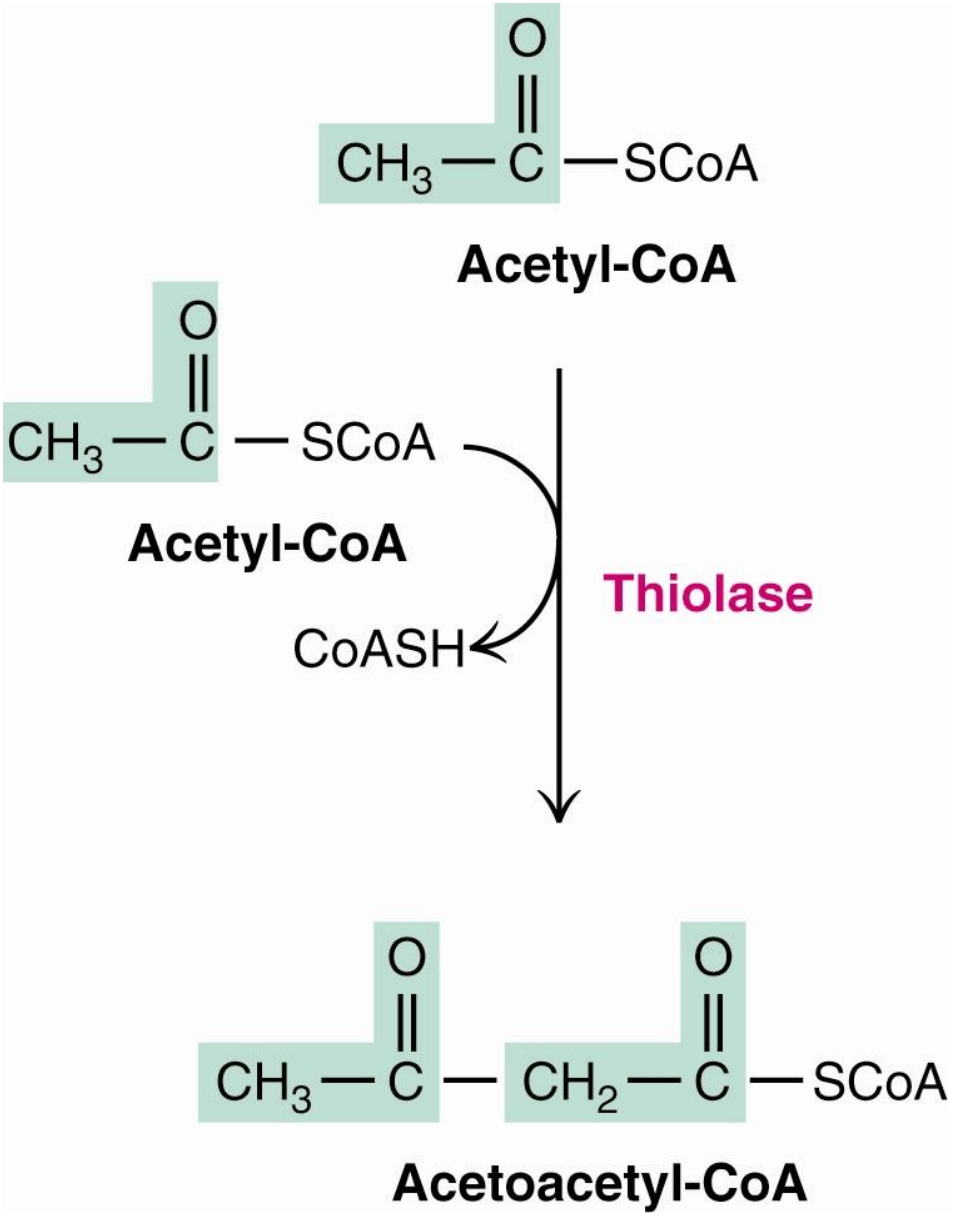


- Biosynthesis begins in the cytosol with the synthesis of mevalonate from acetyl-CoA
- First step is a thiolase reaction
- Second step makes HMG-CoA
- Third step - HMG-CoA reductase - is the rate-limiting step in cholesterol biosynthesis
- HMG-CoA reductase is site of action of cholesterol-lowering drugs

Mevalonate Is Synthesized from Acetyl-CoA Via HMG-CoA Synthase

Figure 24.31 The biosynthesis of 3*R*-mevalonate from acetyl-CoA. The first step is a thiolase-catalyzed Claisen condensation of two molecules of acetyl-CoA to form acetoacetyl-CoA.

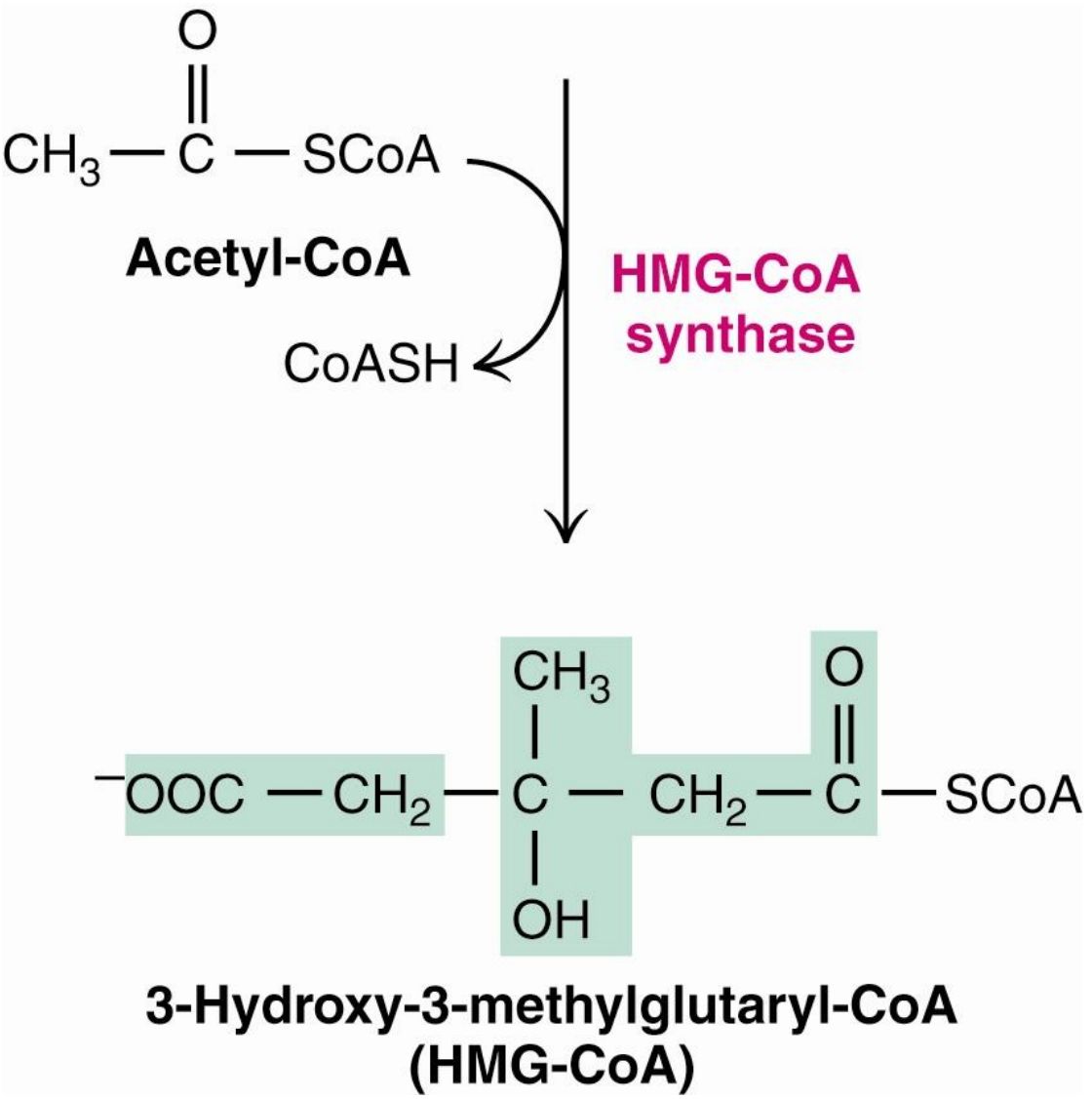
In the next reaction, acetyl-CoA and acetoacetyl-CoA will join to form HMG-CoA.



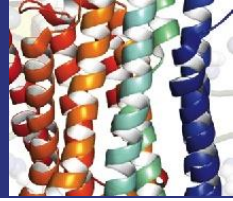
Mevalonate Is Synthesized from Acetyl-CoA Via HMG-CoA Synthase

Figure 24.31The biosynthesis of 3*R*-mevalonate from acetyl-CoA.

In the second reaction, acetyl-CoA and acetoacetyl-CoA join to form HMG-CoA.



Mevalonate Is Synthesized from Acetyl-CoA Via HMG-CoA Reductase



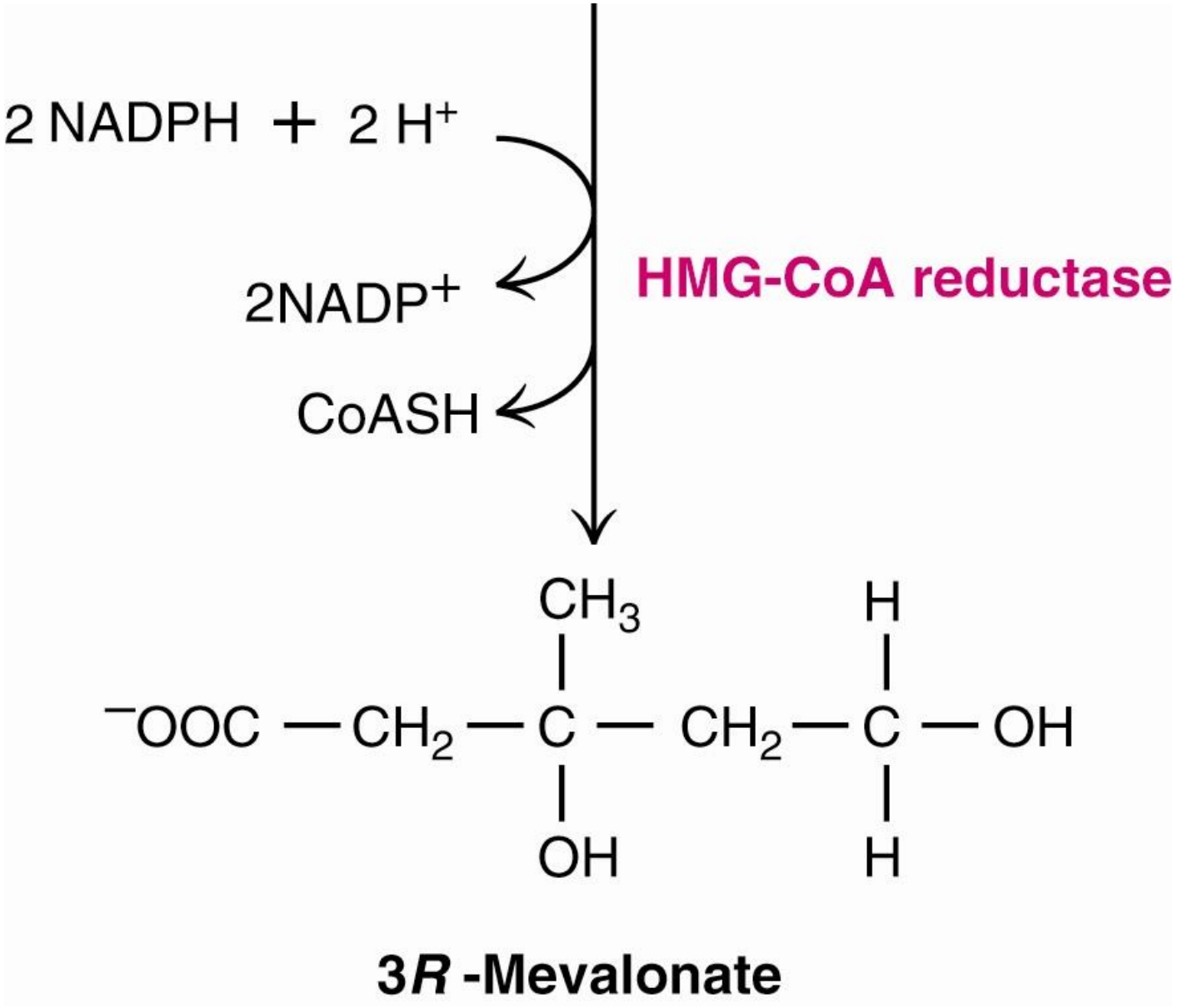


Figure 24.31 HMG-CoA undergoes two NADPH-dependent reductions to produce 3*R*-mevalonate

Mevalonate Is Made from Acetyl-CoA Via HMG-CoA Reductase

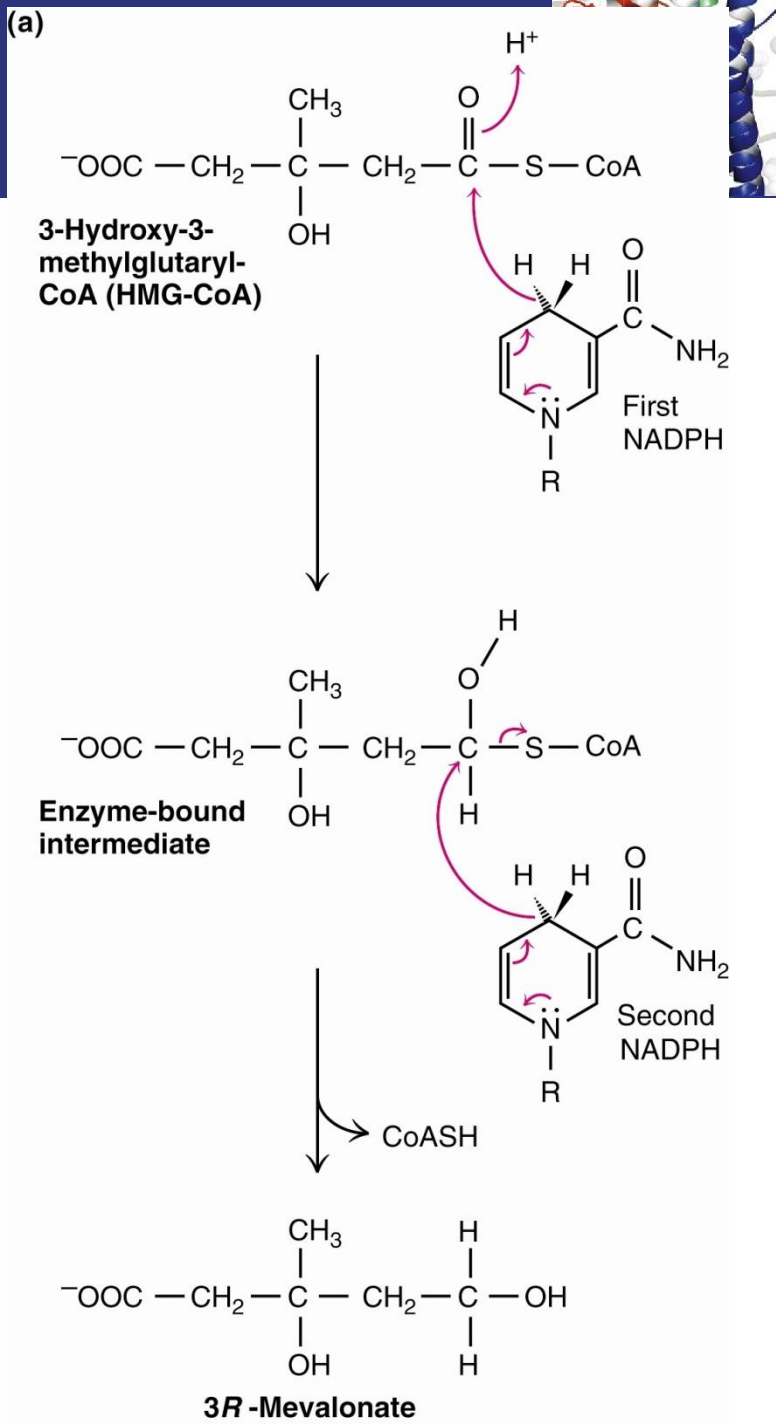
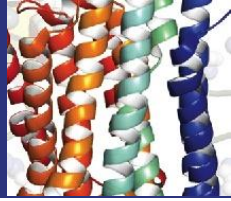


Figure 24.32a A mechanism for HMG-CoA reductase. Two successive NADPH-dependent reductions convert the thioester, HMG-CoA, to a primary alcohol.

Regulation of HMG-CoA Reductase



- *Three different* mechanisms contribute to the regulation of HMG-CoA reductase

1) Phosphorylation by cAMP-dependent protein kinases inactivates the reductase. This inactivation can be reversed by two phosphatases
2) Degradation of HMG-CoA reductase. This enzyme has a half-life of only 3 hours, and the half-life itself depends on cholesterol levels: High [cholesterol] means a short half-life for HMG-CoA reductase
3) Gene expression. Cholesterol levels control the amount of mRNA. If [cholesterol] is high, levels of mRNA coding for the reductase are reduced

Regulation of HMG-CoA Reductase

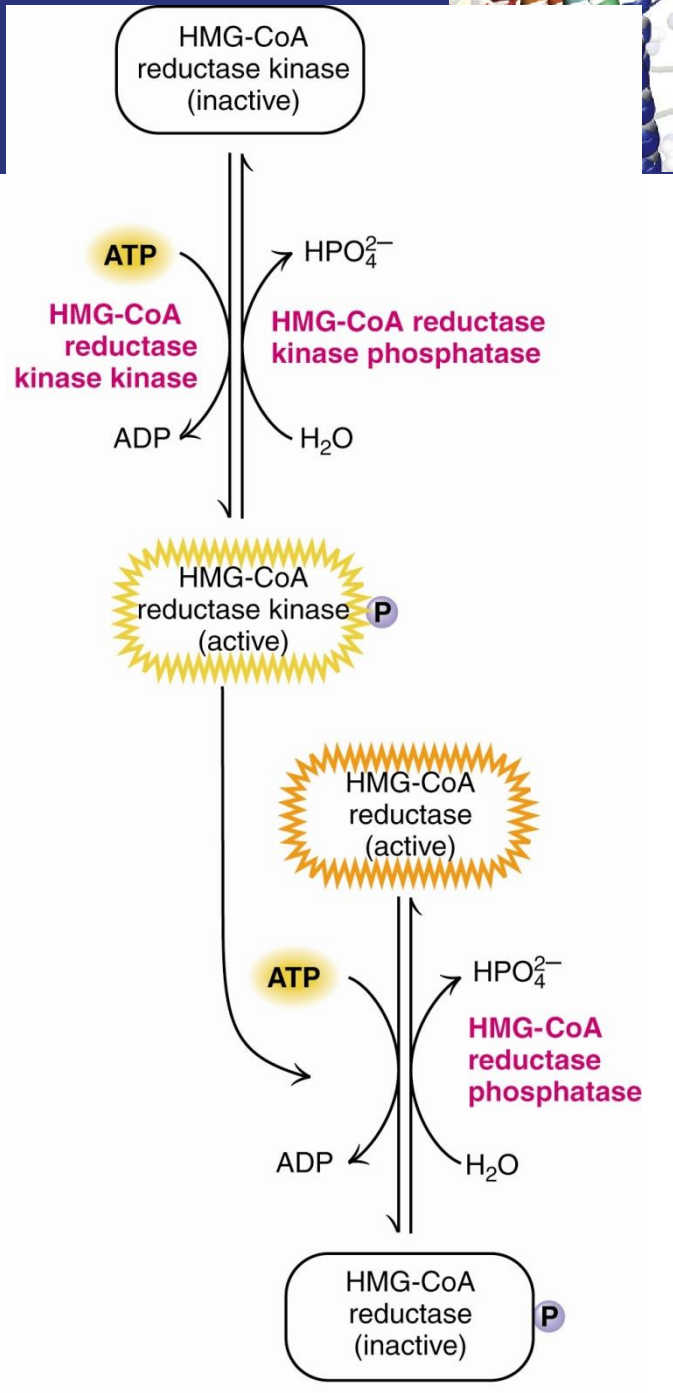
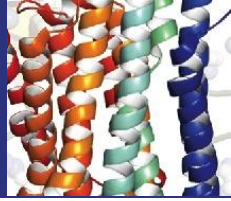


Figure 24.33 HMG-CoA reductase is modulated by phosphorylation and dephosphorylation. The phosphatases involved in dephosphorylation are specific to HMG-CoA reductase.

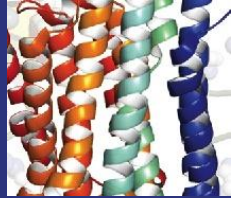
The thiolase brainteaser...



An important puzzle

- If acetate units can be condensed by thiolase to give acetoacetate in the 1st step of cholesterol biosynthesis, why not also use thiolase for FA synthesis, avoiding complexity of FA synthase?
- Solution: Subsequent reactions drive cholesterol synthesis, but eight successive thiolase reactions would be very unfavorable energetically for FA synthesis

Squalene Is Synthesized from Mevalonate



Driven by ATP hydrolysis, decarboxylation and PP_i hydrolysis

- Six-carbon mevalonate makes five carbon **isopentenyl PP_i** and **dimethylallyl PP_i**
- Condensation of 3 of these yields **farnesyl PP_i**
- Two farnesyl PP_i s link to form **squalene**
- Bloch and Langdon were first to show that *squalene is derived from acetate units* and that *cholesterol is derived from squalene*

Squalene Is Synthesized from Mevalonate

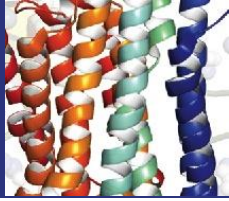
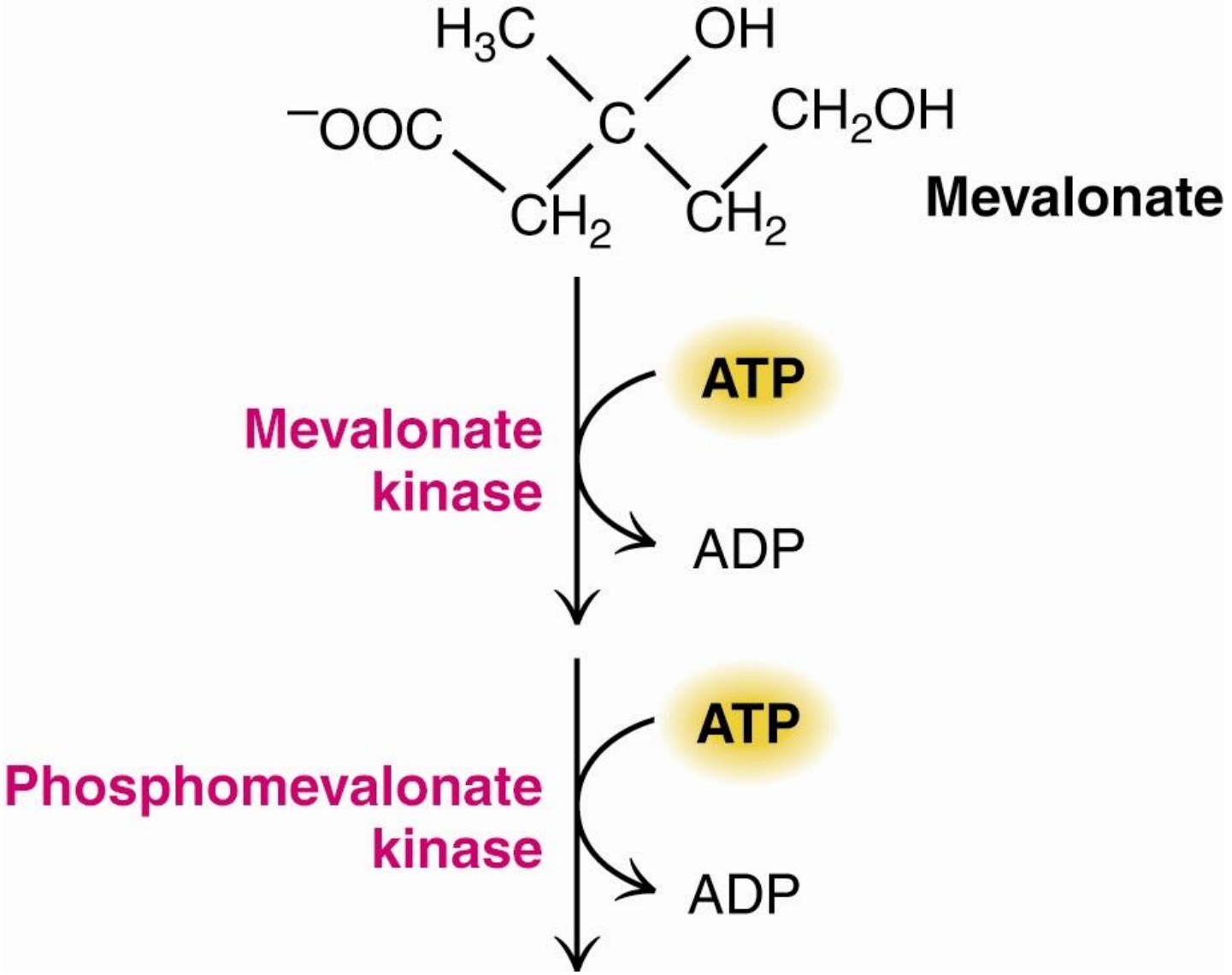


Figure 24.34 The conversion of mevalonate to squalene (frame 1)



Squalene Is Synthesized from Mevalonate

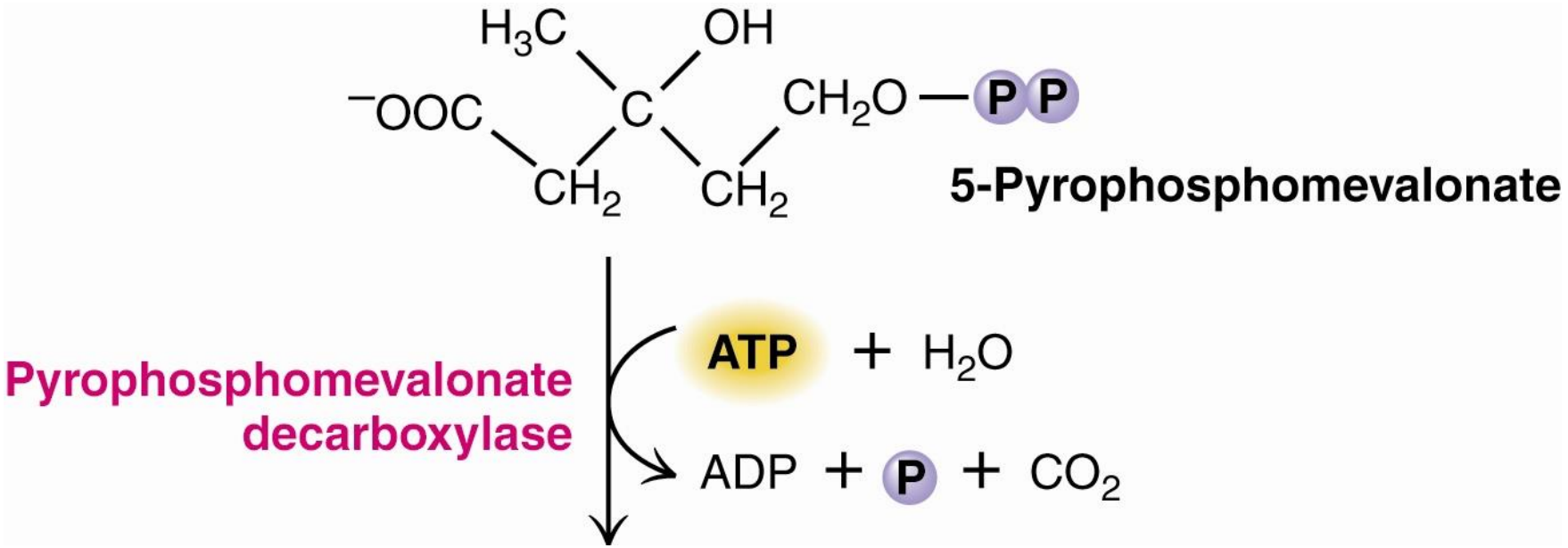


Figure 24.34 The conversion of mevalonate to squalene (frame 2).

Squalene Is Synthesized from Mevalonate

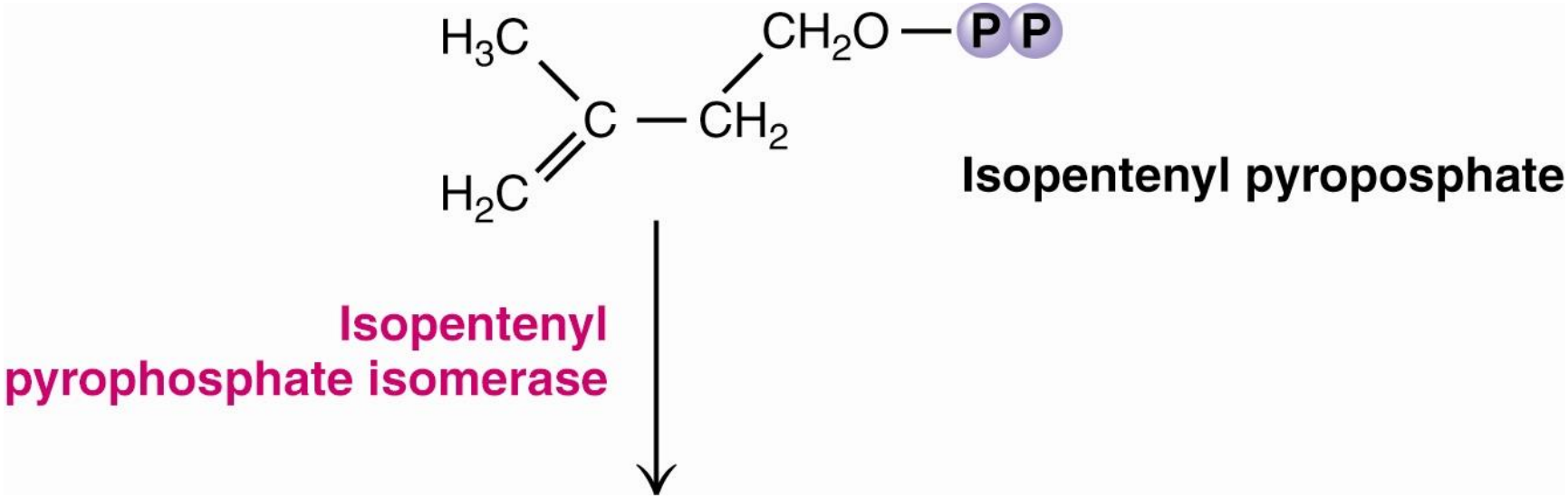


Figure 24.34 The conversion of mevalonate to squalene (frame 3).

Squalene Is Synthesized from Mevalonate

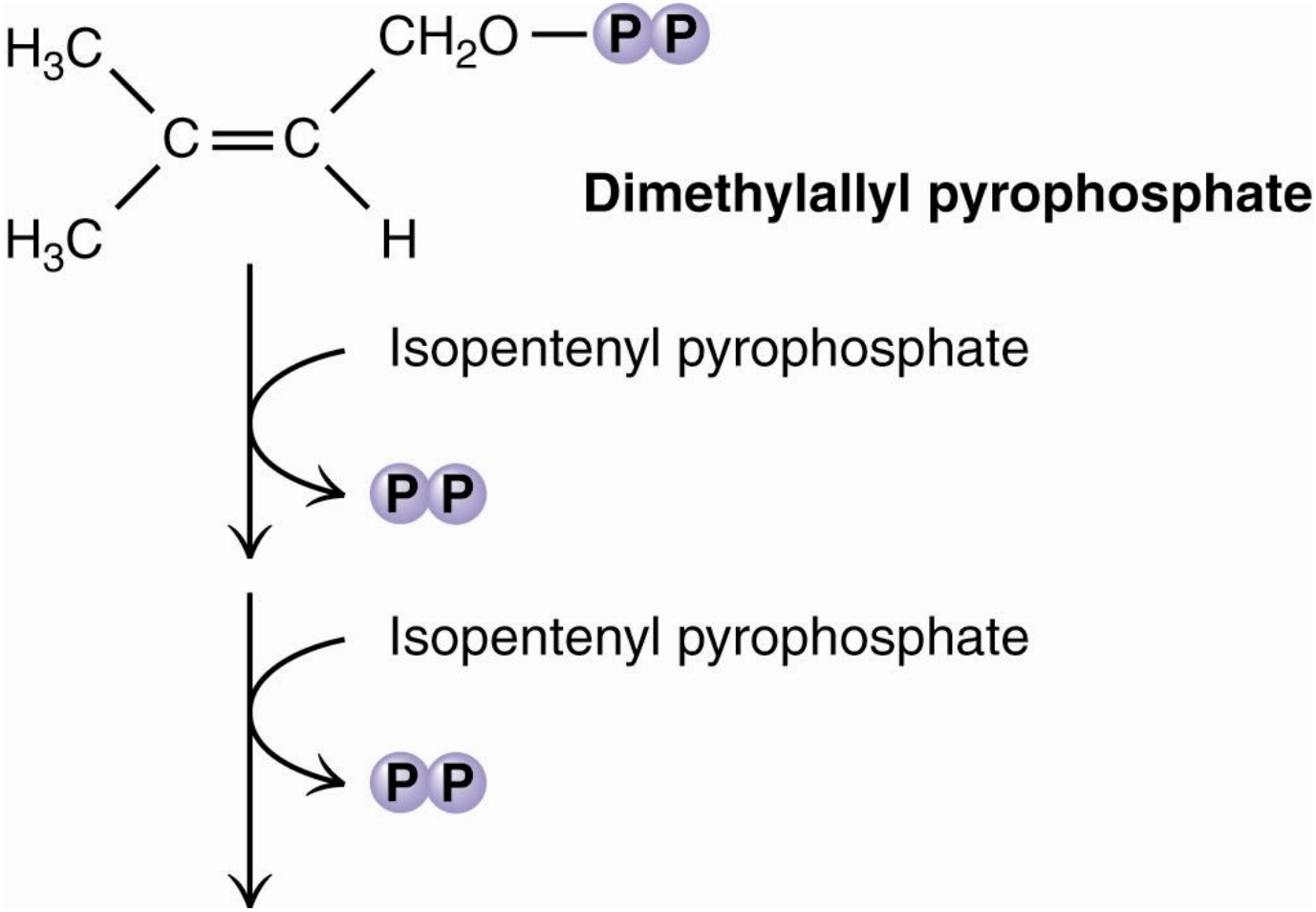


Figure 24.34 The conversion of mevalonate to squalene (frame 4).

Squalene Is Synthesized from Mevalonate

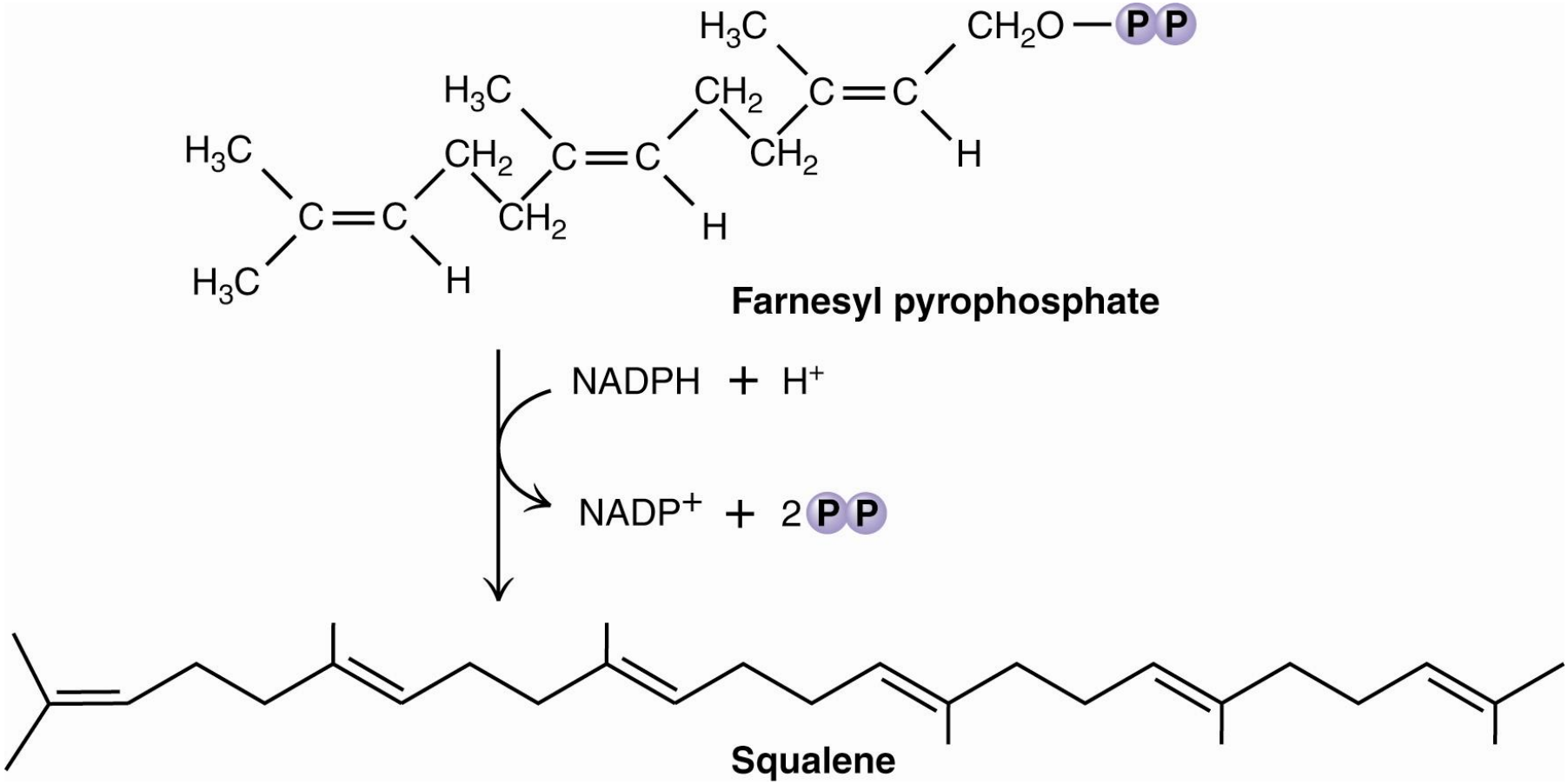
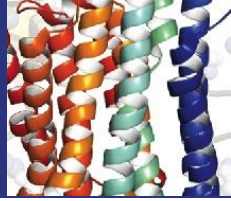


Figure 24.34 The conversion of mevalonate to squalene (frame 5).

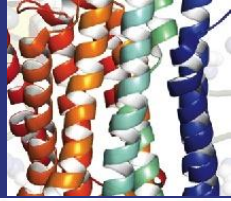
Cholesterol is Formed from Squalene – After Many Steps



*At the **endoplasmic reticulum** membrane*

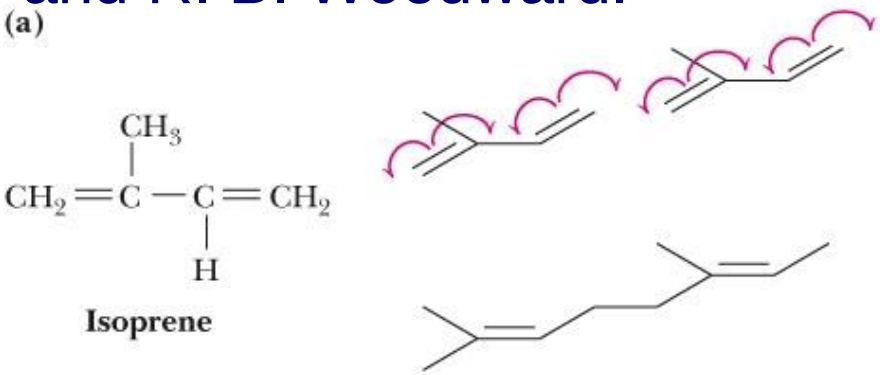
- Squalene monooxygenase converts squalene to **squalene-2,3-epoxide**
- A cyclase converts the epoxide to **lanosterol**
- Though lanosterol looks like cholesterol, 20 more steps are required to form cholesterol
- All at/in the endoplasmic reticulum membrane

The Long Search for the Route of Cholesterol Biosynthesis



In 1952, Konrad Bloch and Robert Langdon showed conclusively that labeled squalene is synthesized rapidly from labeled acetate, and also that cholesterol is derived from squalene.

(a) An isoprene unit and a scheme for head-to-tail linking of isoprenes. (b) The cyclization of squalene to form lanosterol, as first proposed by Bloch and R. B. Woodward.



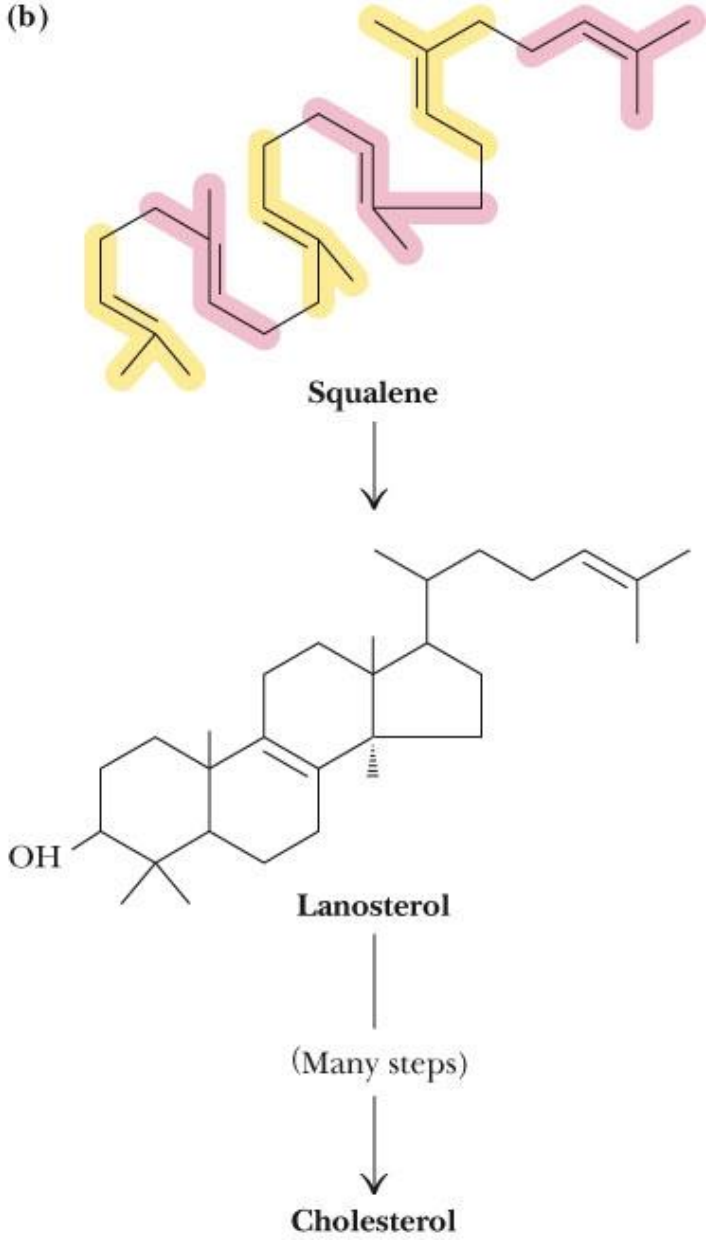


Figure 24.35 This conversion requires FAD and NADPH as coenzymes and requires O_2 as well as a cytosolic protein called soluble protein activator. A cyclase catalyzes the second reaction, which involves a succession of 1,2 shifts of hydride ions and methyl groups.

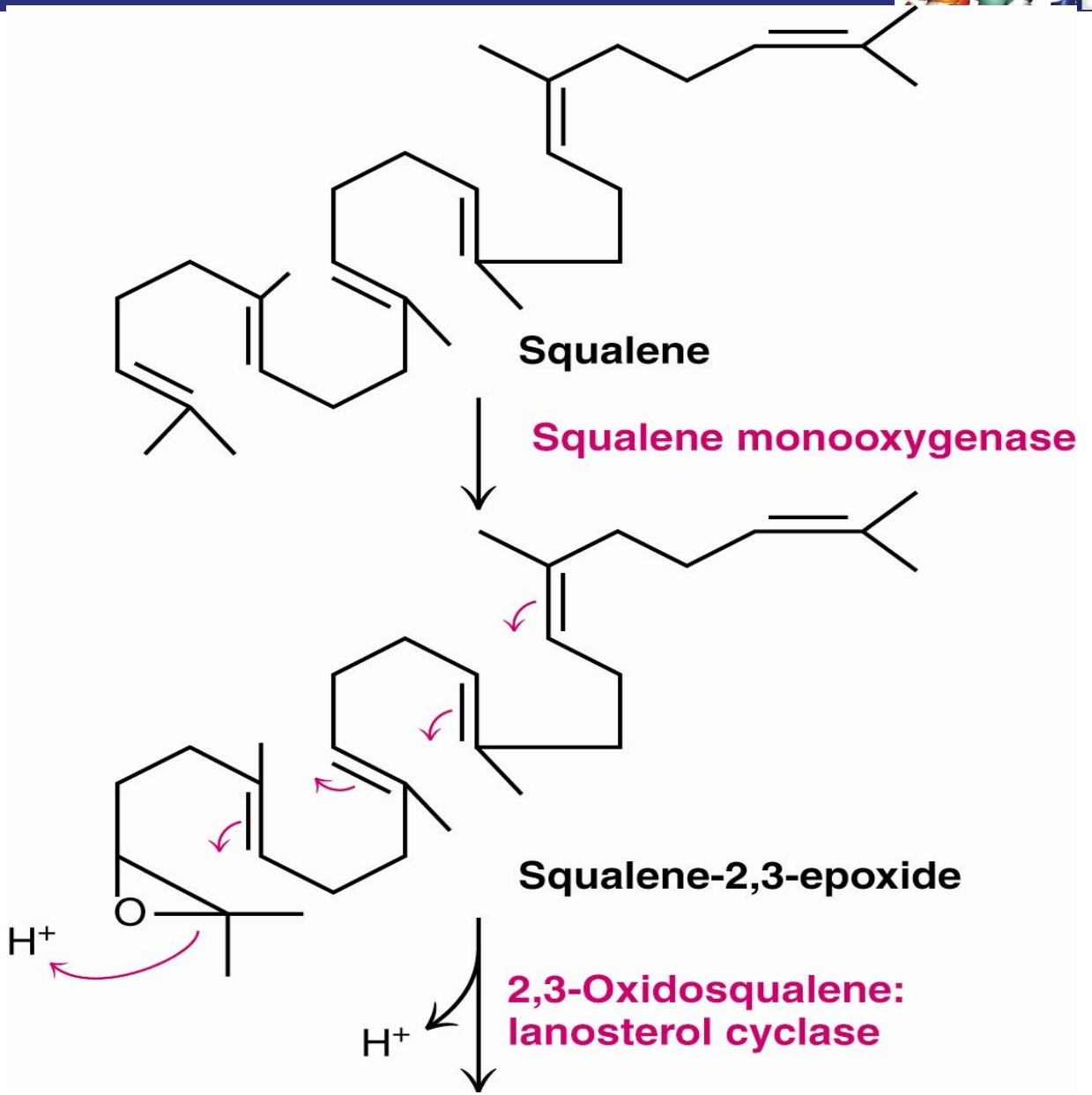
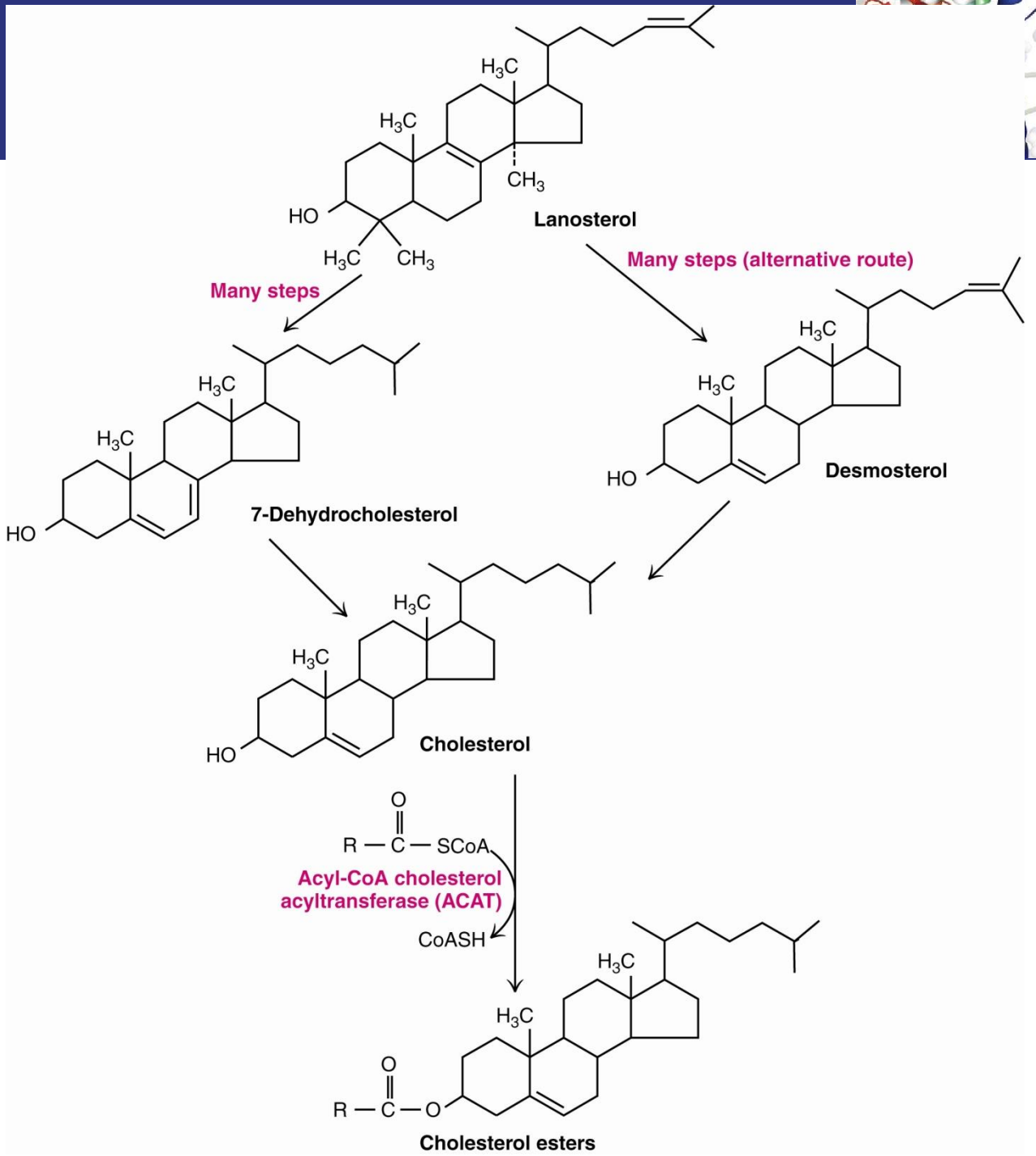
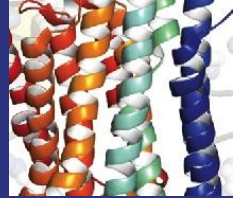


Figure 24.35. Twenty steps are required to convert lanosterol to cholesterol The enzymes ar all associated with the endoplasmic reticulum.

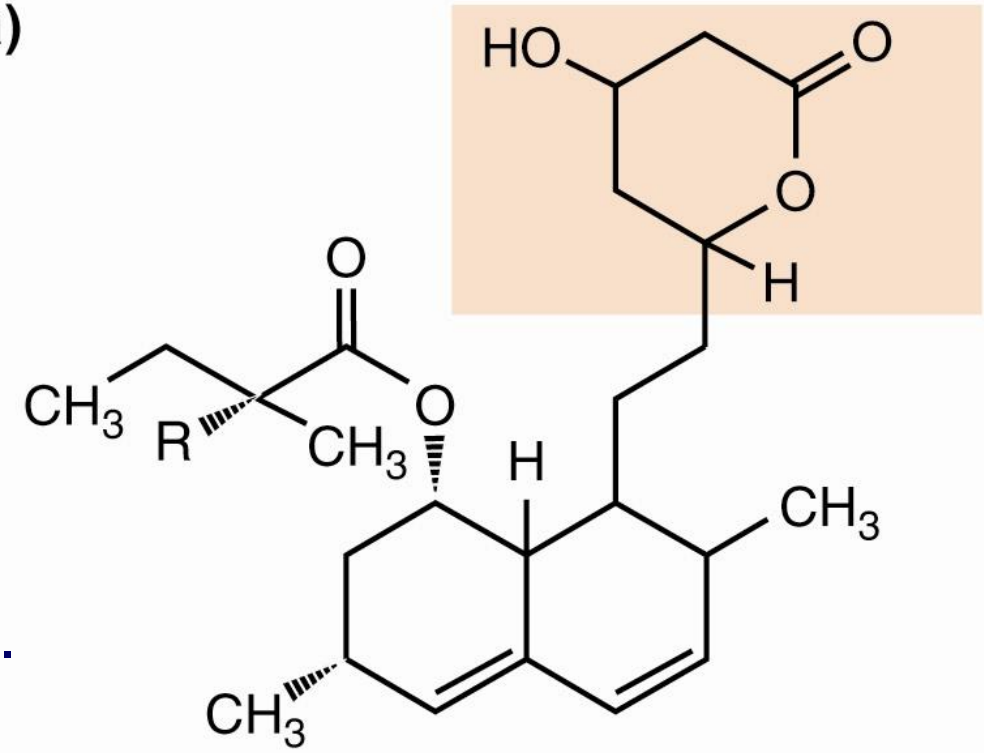


Statins Lower Serum Cholesterol Levels



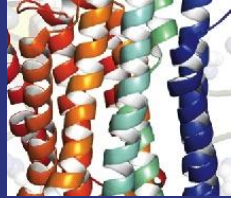
HMG-CoA reductase is the rate-limiting step in cholesterol synthesis. As such, it is a likely drug target. Mevinolin and similar drugs are cholesterol lowering drugs that act as transition state analogs, binding like transition states to the HMG-CoA reductase.

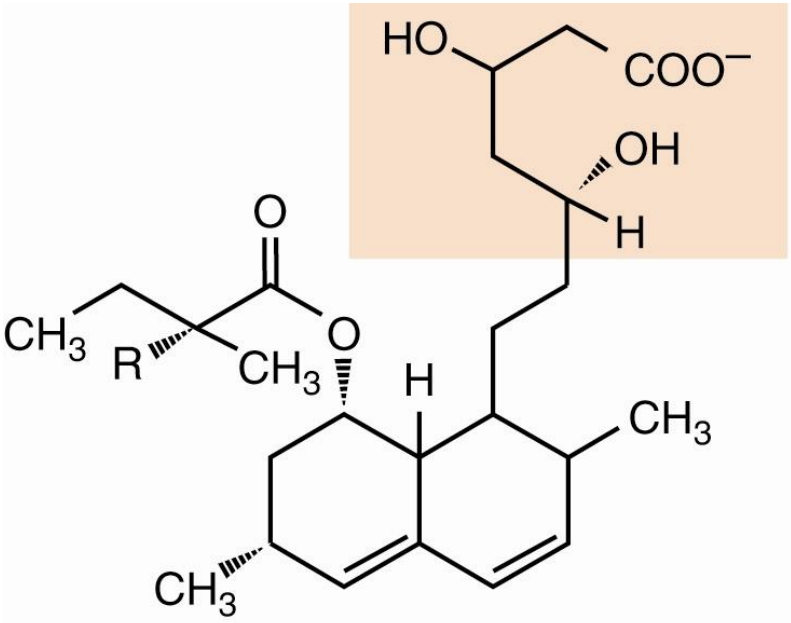
(a)



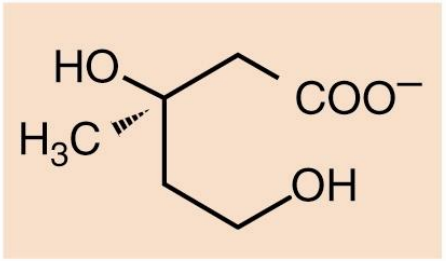
1 R=H Mevinolin (Lovastatin, MEVACOR®)
2 R=CH_3 Synvinolin (Simvastatin, ZOCOR®)

Statins Lower Serum Cholesterol Levels

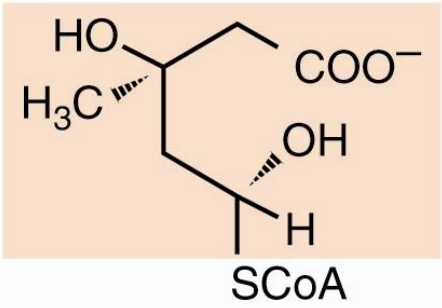




Mevinolinic acid



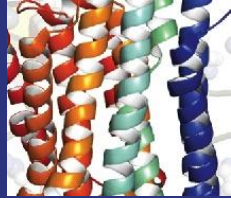
Mevalonate



Tetrahedral intermediate in HMG-CoA reductase mechanism

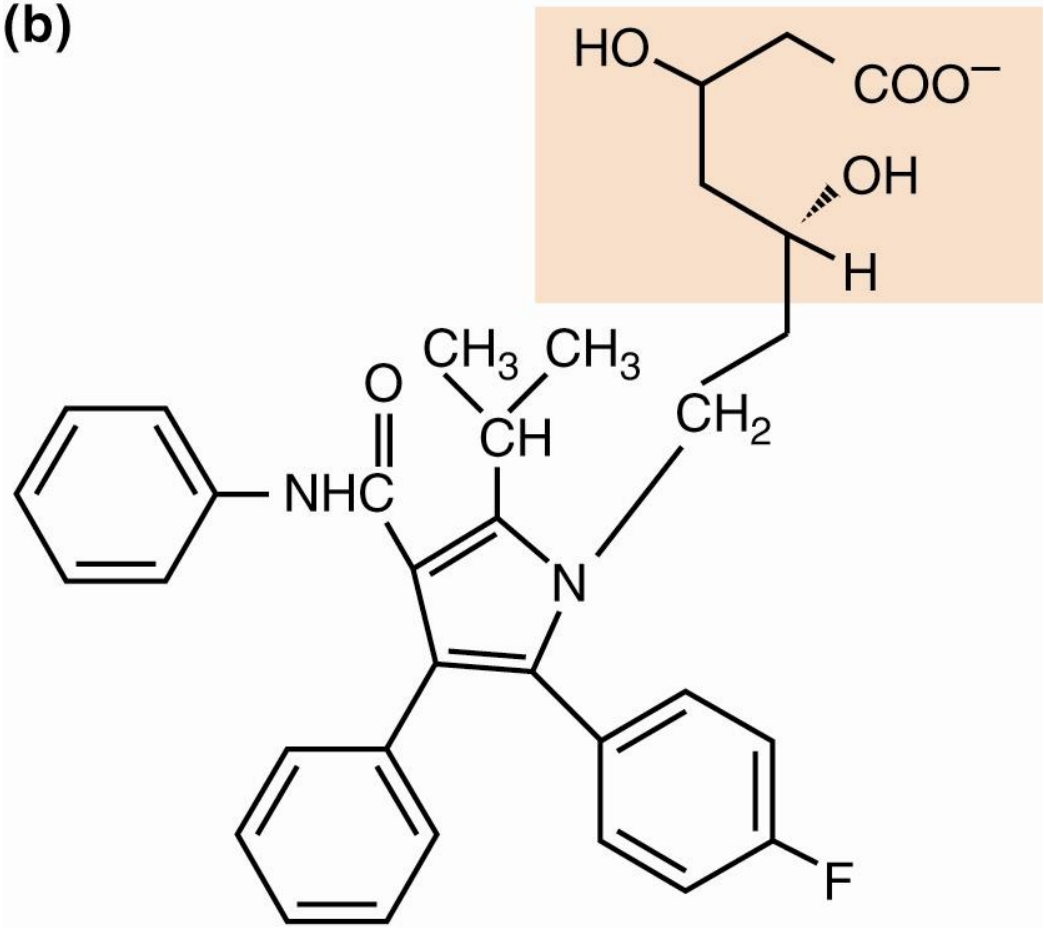
The structure of mevinolinic acid compared with the structure of mevalonate and the tetrahedral intermediate in the mechanism of HMG-CoA reductase. Mevinolin is converted to mevinolinic acid (a transition state analog) in the body.

Statins Lower Serum Cholesterol Levels



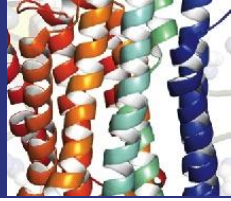
For several years, Lipitor has been the best-selling drug in the world, with annual sales exceeding $10 Billion.

(b)



Lipitor®
(Atorvastatin)

24.5 How Are Lipids Transported Throughout the Body?



Lipoproteins are the carriers of most lipids in the body

- **Lipoprotein** - a cluster of lipids, often with a monolayer membrane, together with an apolipoprotein
- See Table 24.1 on lipoproteins
- **HDL**, **VLDL** assemble in the ER of liver cells
- **Chylomicrons** form in the intestines
- **LDL** not made directly, but evolves from VLDL

24.5 How Are Lipids Transported Throughout the Body?

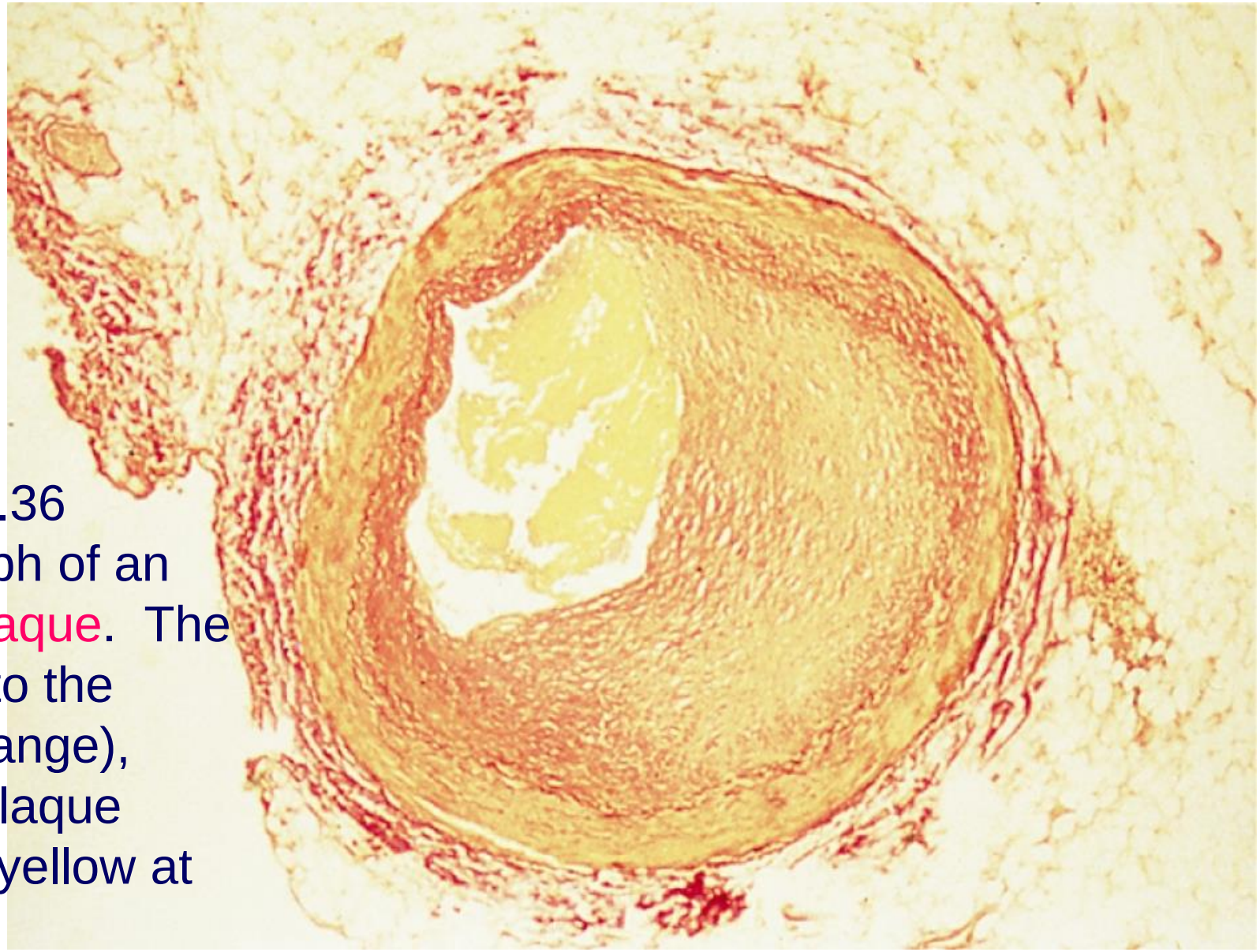


Figure 24.36
Photograph of an arterial plaque. The view is into the artery (orange), with the plaque shown in yellow at the back.

24.5 How Are Lipids Transported Throughout the Body?

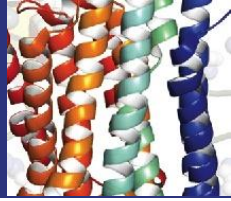
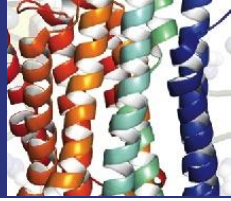


TABLE 24.1 Composition and Properties of Human Lipoproteins

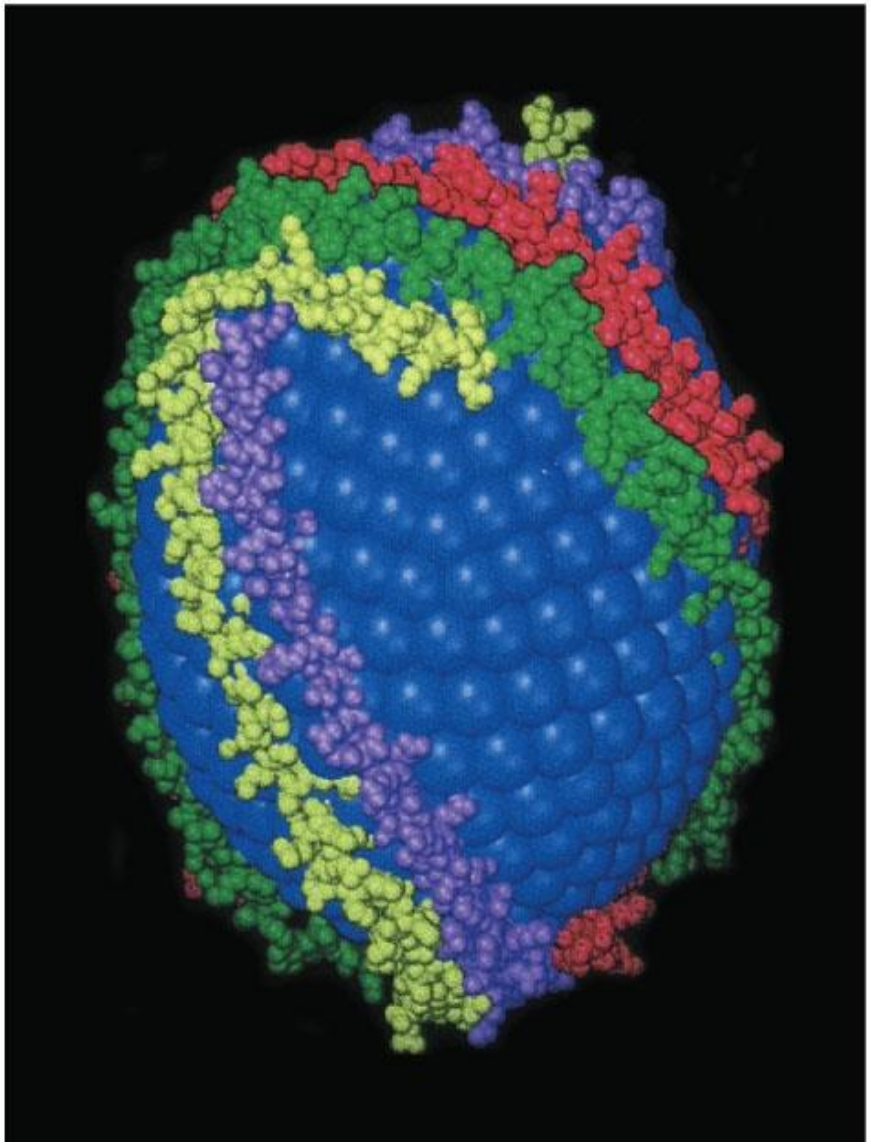
Lipoprotein Class	Density (g/mL)	Diameter (nm)	Composition (% dry weight)			
			Protein	Cholesterol	Phospholipid	Triacylglycerol
HDL	1.063–1.21	5–15	33	30	29	8
LDL	1.019–1.063	18–28	25	50	21	4
IDL	1.006–1.019	25–50	18	29	22	31
VLDL	0.95–1.006	30–80	10	22	18	50
Chylomicrons	<0.95	100–500	1–2	8	7	84

Table 24.1 It is customary to classify lipoproteins according to their densities. The densities are related to the relative amounts of lipid and protein in the complexes. Most proteins have densities of about 1.3 to 1.4 g/mL, and lipid aggregates usually possess densities of about 0.8 g/mL, the more protein and the less lipid in a complex, the denser the lipoprotein.

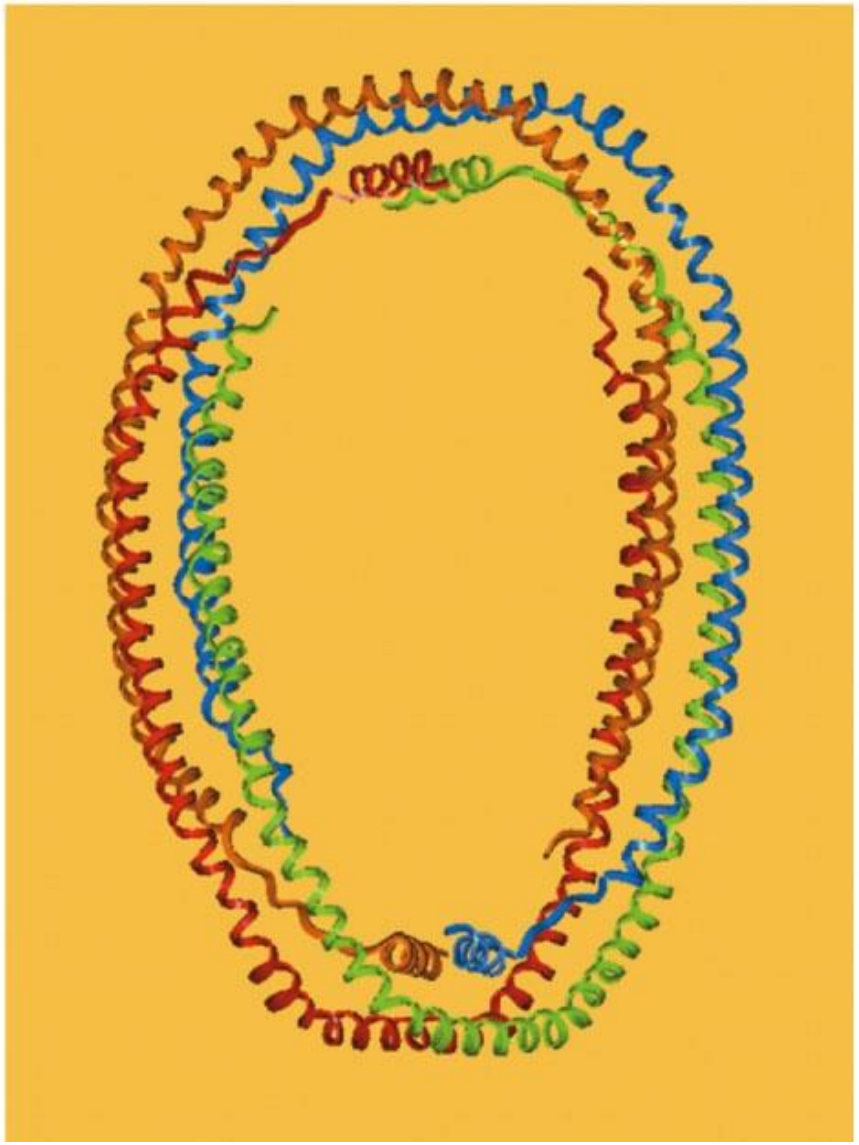
Figure 24.37 A Model for the Structure of a Typical Lipoprotein.



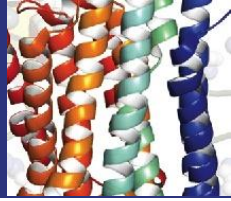
(a)



(b)



Lipoproteins in Circulation Are Progressively Degraded by Lipoprotein Lipase



- In the capillaries of muscle and adipose cells, **lipoprotein lipases** hydrolyze triglycerides from lipoproteins, making the lipoproteins smaller and raising their density
- Thus chylomicrons and VLDLs are progressively converted to IDL and then LDL, which either return to the liver for reprocessing or are redirected to adipose tissues and adrenal glands

A Number of Different Apoproteins Have Been Identified in Lipoproteins

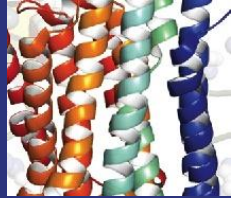


TABLE 24.2 Apoproteins of Human Lipoproteins

Apoprotein	M_r	Concentration in Plasma (mg/100 mL)	Distribution
A-1	28,300	90–120	Principal protein in HDL
A-2	8,700	30–50	Occurs as dimer mainly in HDL
B-48	240,000	<5	Found only in chylomicrons
B100	500,000	80–100	Principal protein in LDL
C-1	7,000	4–7	Found in chylomicrons, VLDL, HDL
C-2	8,800	3–8	Found in chylomicrons, VLDL, HDL
C-3	8,800	8–15	Found in chylomicrons, VLDL, IDL, HDL
D	32,500	8–10	Found in HDL
E	34,100	3–6	Found in chylomicrons, VLDL, IDL, HDL

The various apoproteins have an abundance of hydrophobic amino acid residues, as is appropriate for interactions with lipids.

Lipoprotein Components Are Synthesized Predominantly in the ER of Liver Cells

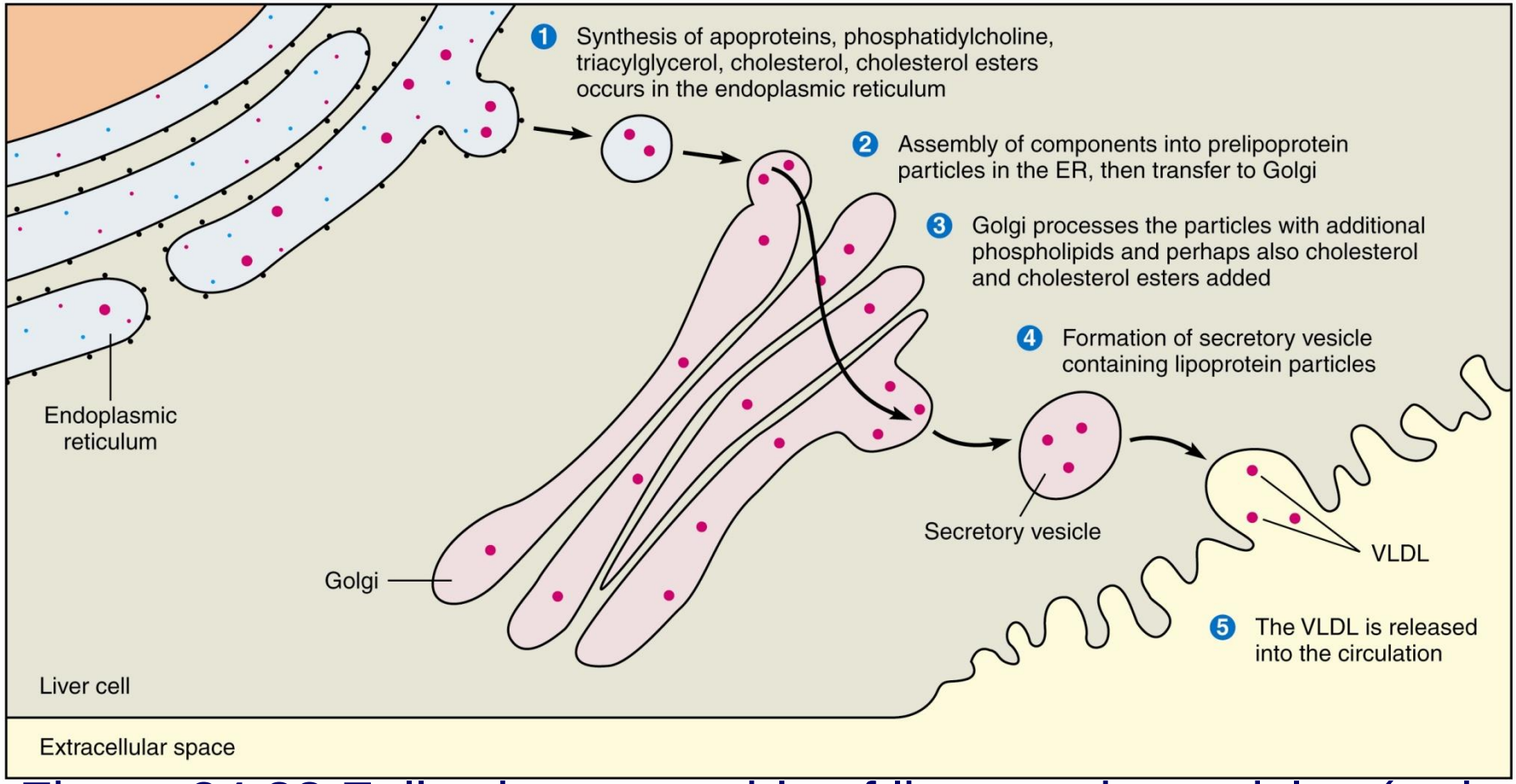


Figure 24.38 Following assembly of lipoprotein particles (red dots) in the ER and processing in the Golgi, lipoproteins are packaged in secretory vesicles for export from the cell.

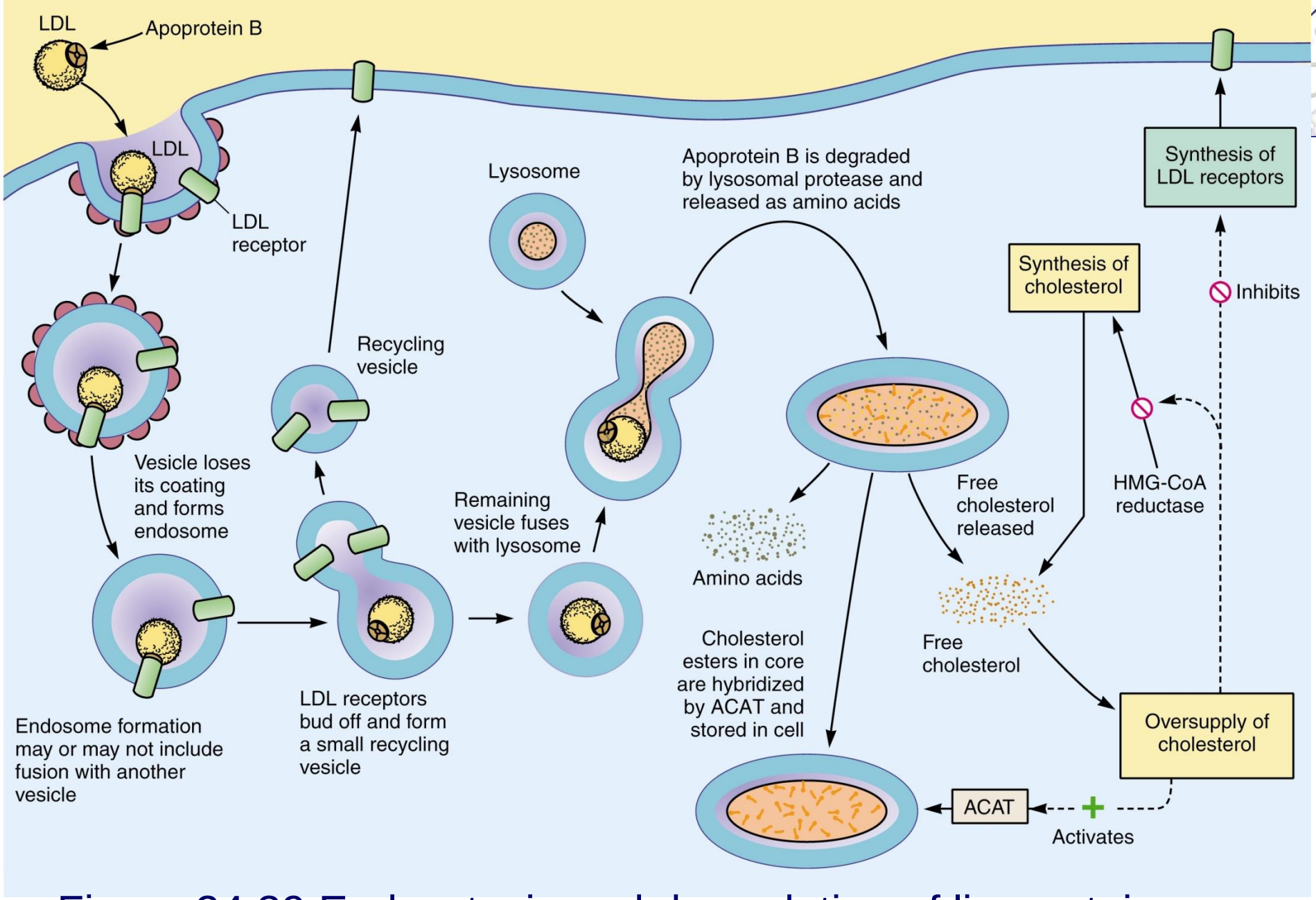
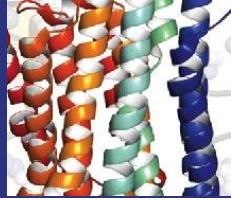


Figure 24.39 Endocytosis and degradation of lipoprotein particles. (ACAT is acyl-CoA cholesterol acyltransferase.)

Structure of the LDL Receptor Involves Five Domains



The LDL receptor is a complex plasma membrane protein

- The LDL receptor in plasma membranes consists of 839 amino acid residues and is composed of five domains

1) LDL binding domain on N-terminus

2, 3)N-linked and O-linked oligosaccharide domains

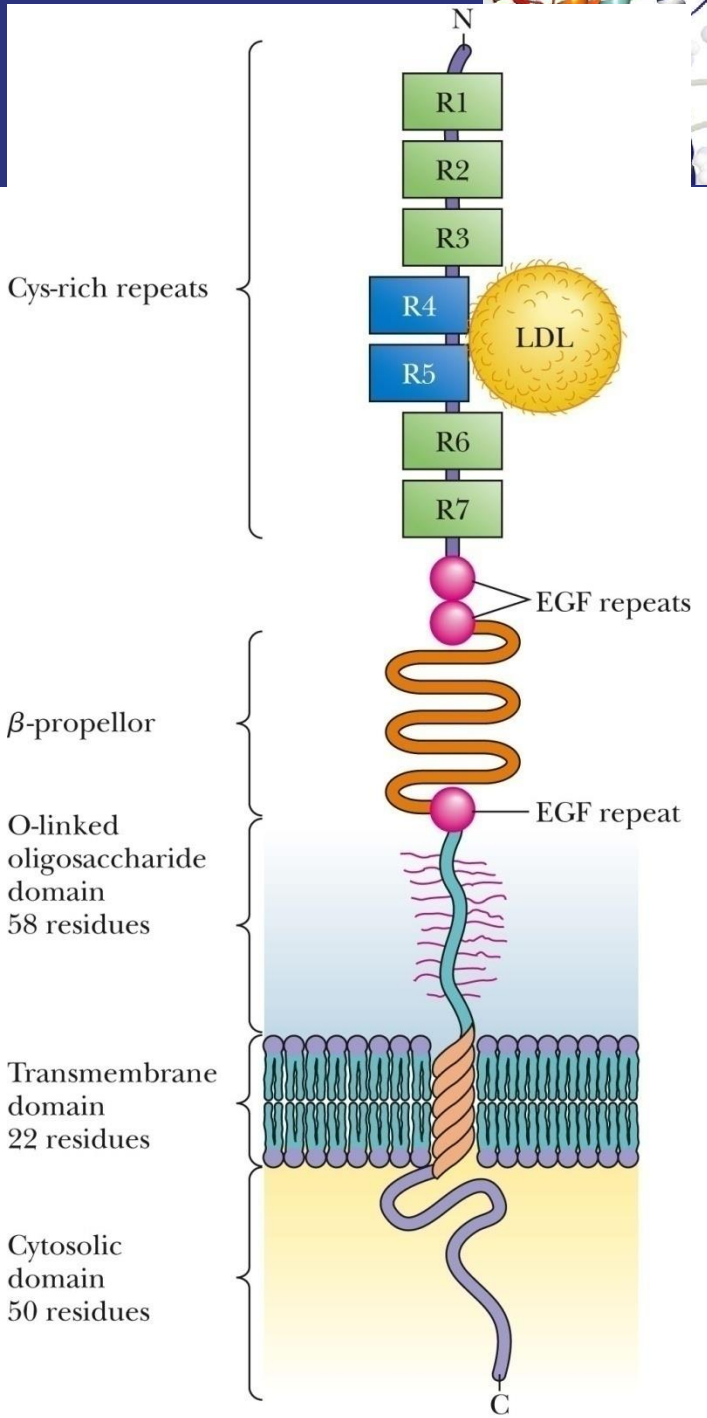
4) A single transmembrane segment

5) A cytosolic domain essential to aggregation of receptors in the membrane during endocytosis

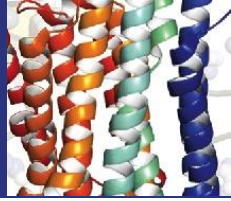
- Dysfunctions in or absence of LDL receptors lead to familial hypercholesterolemia

Structure of the LDL Receptor Involves Five Domains

Figure 24.40 The structure of the LDL receptor. The amino-terminal binding domain is responsible for recognition and binding of LDL apoprotein. The B-100 apolipoprotein of the LDL particle is presumed to bind to the fourth and fifth cysteine-rich repeats (R4 and R5). The O-linked oligosaccharide-rich domain may act as a molecular spacer, raising the binding domain above the glycocalyx. The cytosolic domain is required for aggregation of LDL receptors during endocytosis.



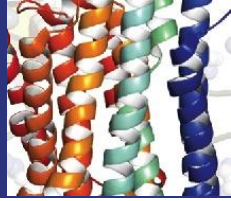
Defects in Lipoprotein Metabolism Can Lead to Elevated Serum Cholesterol



The division of labor

- Chylomicrons' main task is to carry triglycerides
- LDLs are principal carriers of cholesterol and cholesterol esters
- Relative amounts of HDL and LDL affect disposition of cholesterol and formation of arterial plaques
- The cholesterol/HDL ratio is key: greater than 4.5 is a risk factor for heart disease
- **Familial hypercholesterolemia** is the term given to a variety of inherited metabolic defects that lead to greatly elevated levels of serum cholesterol, much of it in the form of LDL particles

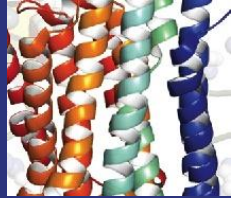
Typical values for HDL, LDL



For males, females, age15-29

- Cholesterol: females - 157-167, males - 150-174
- HDL: females - 52-55, males 45
- LDL: females - 100-106, males 97-116
- However, with age, total cholesterol rises, and HDLs may fall, so exercise and diet become key
- Regular, vigorous exercise raises HDLs and a low fat diet that avoids red meat reduces serum cholesterol levels

24.6 How Are Bile Acids Biosynthesized?



- **Bile acids** are polar carboxylic acid derivatives of cholesterol
- They are essential for the digestion of food, especially for solubilization of ingested fats
- Synthesized from cholesterol
- **Cholic acid** conjugates with taurine and glycine to form **taurocholic** and **glycocholic acids**
- First step is oxidation of cholesterol by a **mixed-function oxidase**
- The formation of bile salts represents the major pathway for cholesterol degradation

24.6 How Are Bile Acids Biosynthesized?

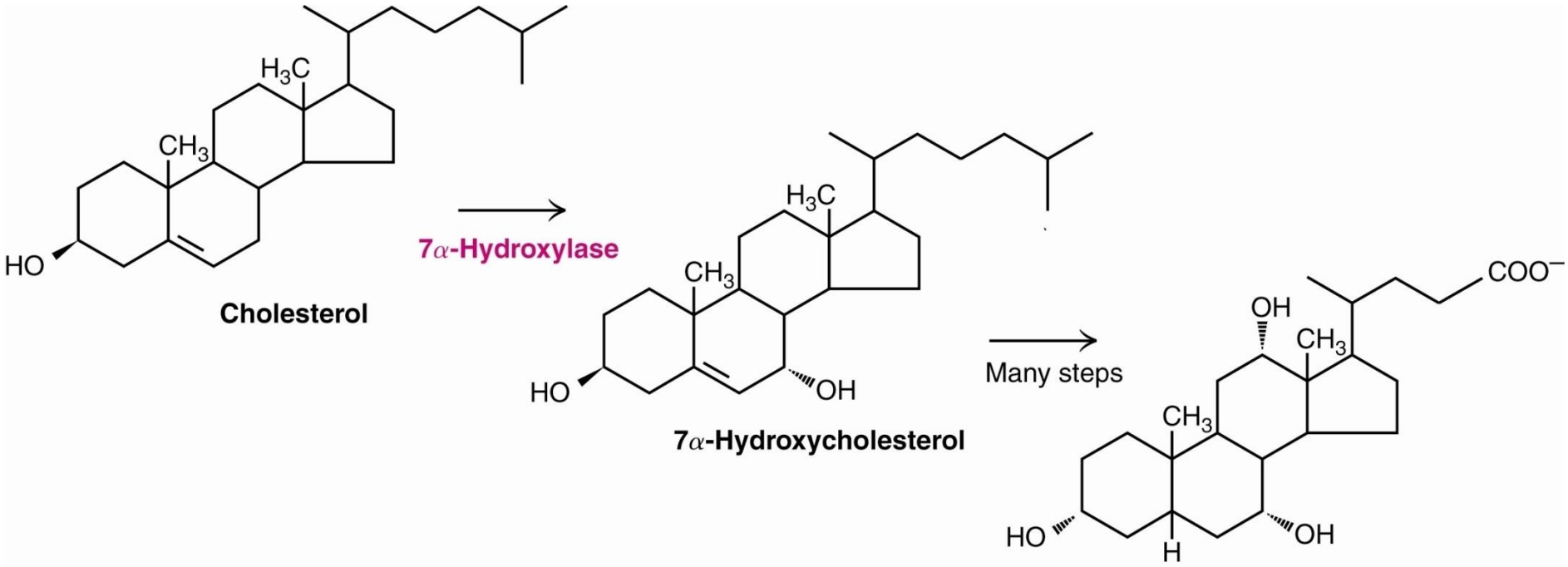
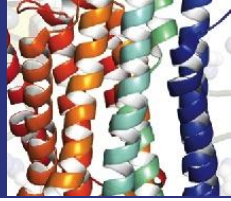


Figure 24.42 Cholic acid, a bile salt, is synthesized from cholesterol via 7α-hydroxycholesterol. Conjugation with taurine or glycine produces taurocholic acid and glycocholic acid, respectively. Taurocholate and glycocholate are freely water soluble and are highly effective detergents.

24.6 How Are Bile Acids Biosynthesized?



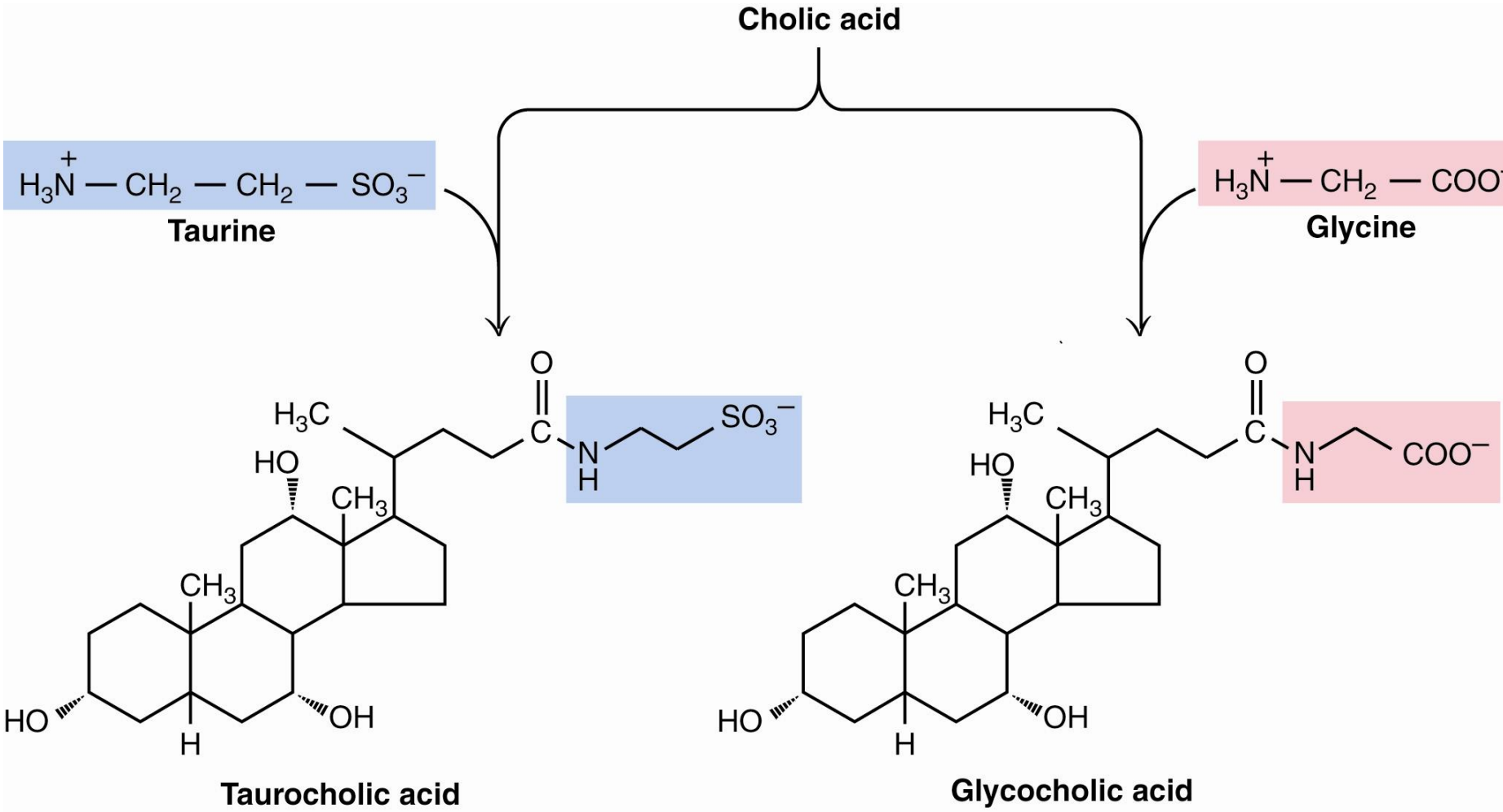
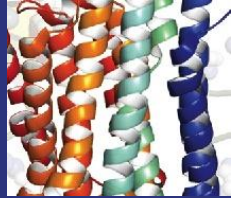


Figure 24.42 Conjugation with taurine or glycine produces taurocholic acid and glycocholic acid, respectively. Taurocholate and glycocholate are freely water soluble and are highly effective detergents.

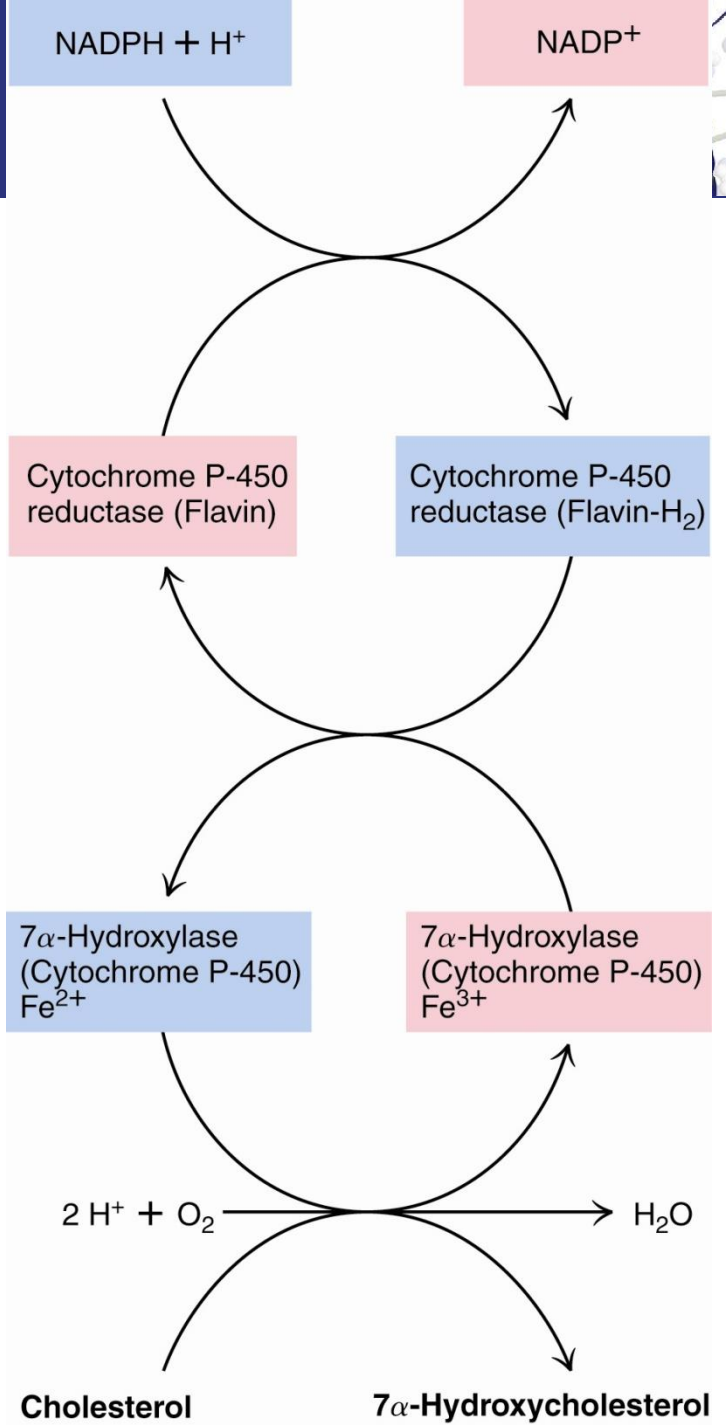
24.7 How Are Steroid Hormones Synthesized and Utilized?



- Steroid hormones are crucial signal molecules
- Biosynthesis begins with the desmolase reaction (in mitochondria), which forms **pregnenolone**, precursor to all others
- Pregnenolone migrates from mitochondria to ER where progesterone is formed
- **Progesterone** is a branch point - it produces **sex steroids** (testosterone and estradiol), and **corticosteroids** (cortisol and aldosterone)
- **Anabolic steroids** are illegal and dangerous
- Recall the stories of Ben Johnson, Marion Jones, and many others…

24.7 How Are Steroid Hormones Synthesized and Utilized?

Figure 24.43 The mixed-function oxidase activity of **7α-hydroxylase**. Mixed function oxidases use O_2 as a substrate and also involve **cytochrome P-450**.



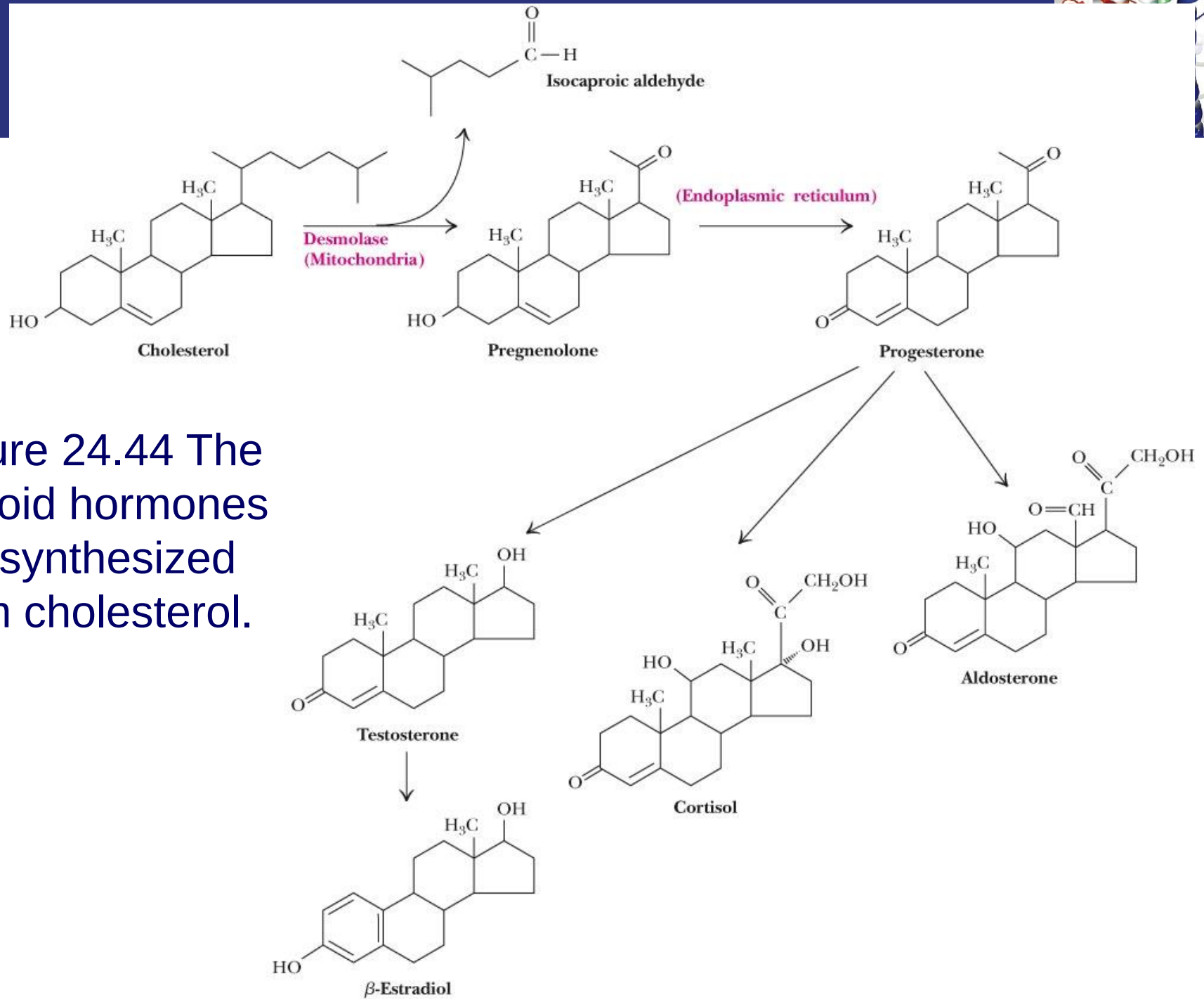
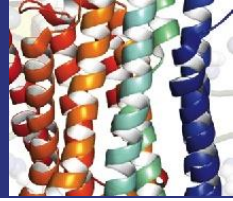
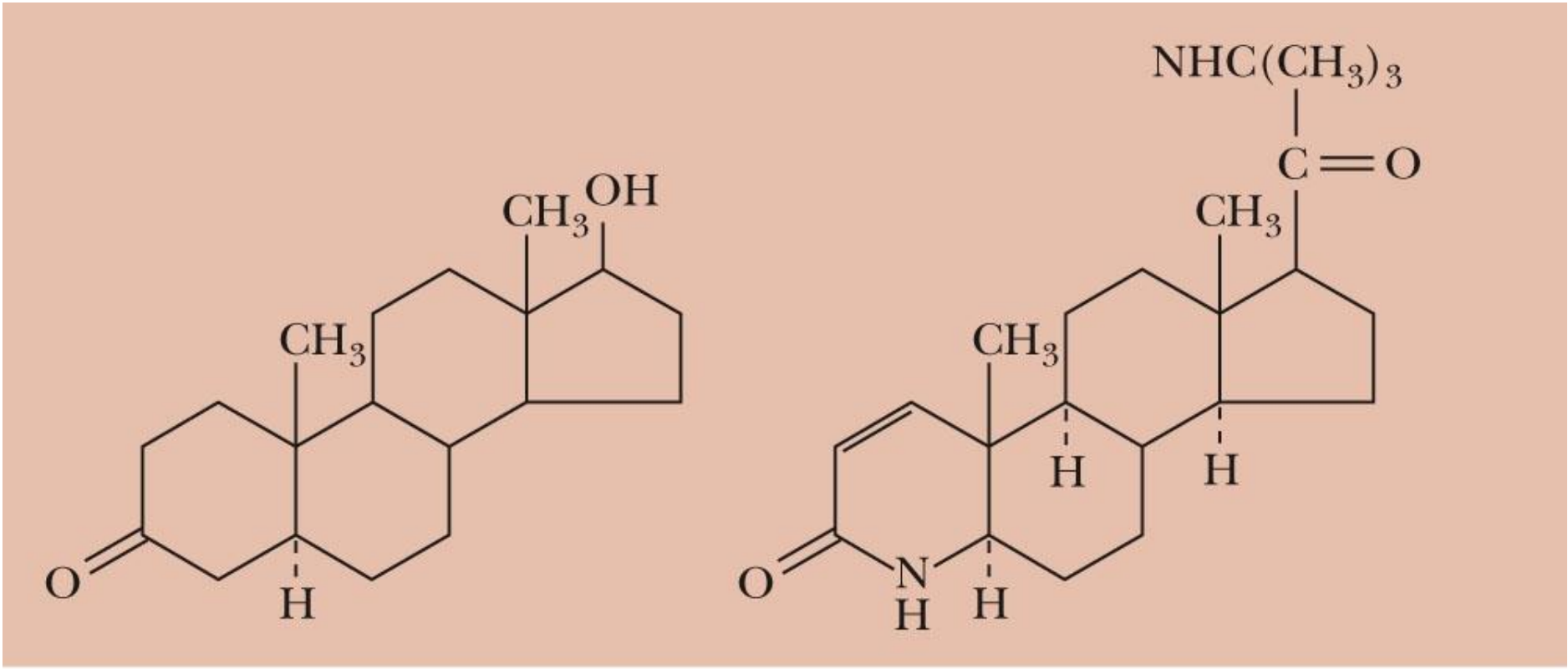


Figure 24.44 The steroid hormones are synthesized from cholesterol.

Steroid 5α-Reductase is a Factor in Male Baldness and Prostatic Cancer





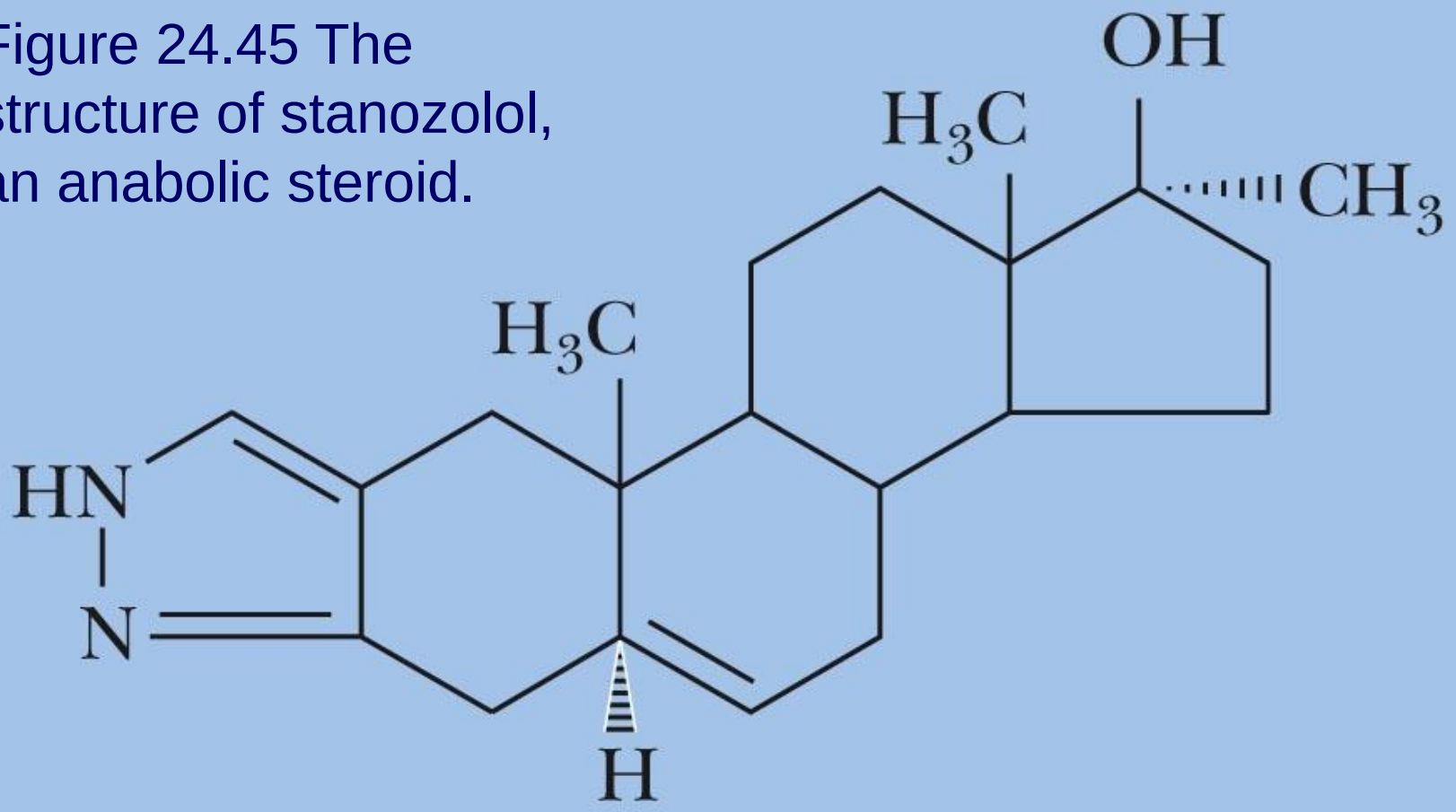
Dihydrotestosterone

Finasteride

Steroid 5α-Reductases are membrane-bound enzymes that catalyze NADPH-dependent reduction of testosterone to dihydrotestosterone (above). Finasteride is a specific inhibitor of type II 5α-reductase.

Anabolic Steroids Have Been Used Illegally to Enhance Athletic Performance

Figure 24.45 The structure of stanozolol, an anabolic steroid.



Stanozolol